The American Journal of Medicine

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Change of address must reach us one month preceding month of issue.

invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

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Phenobarbital	1/8 gr.

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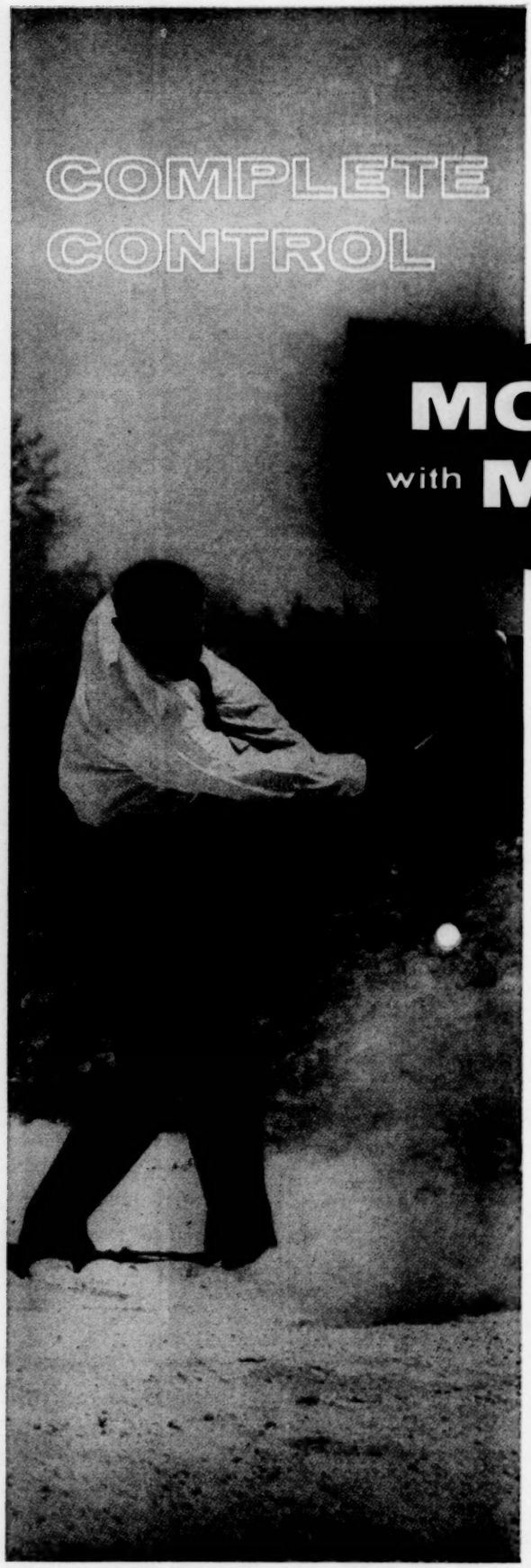

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CONTENTS

The American Journal of Medicine

Vol. XXI AUGUST, 1956 No. 2

Editorial

Clinical Studies

The etiology of a large segment of undifferentiated acute respiratory diseases appears to have been established by the recent discovery of RI viruses, also designated APC viruses. The present study adds additional evidence in support of this contention by demonstrating the type 7 RI virus etiology of forty-five cases of respiratory illness contracted in an epidemic. The basic syndrome in this epidemic was characterized by fever, exudative pharyngitis and cough, in more severe cases accompanied by conjunctivitis, rhinitis, catarrhal otitis, laryngitis, bronchiolitis and pneumonitis. Probably what has been designated pharyngoconjunctival fever, non-streptococcic exudative pharyngitis and primary atypical pneumonia (without cold or streptococcus MG agglutinins) belong in this category but the true common cold and serologically distinct primary atypical pneumonia, among other discrete respiratory diseases, do not.

While viruses of the Coxsackie group are now generally recognized to be the causative agent of herpangina and pleurodynia, their role in other presumed virus diseases, particularly in the adult, remains in doubt. Indeed, there is confusion as to the pathologic significance of isolation of these viruses in sick patients since the notion has become prevalent that Coxsackie viruses are ubiquitous. Dr. Kilbourne has undertaken the prodigious task of clarifying all this, and the results are of unusual interest. He finds that the occurrence of viruses of the Coxsackie group is not indiscriminate but selective. Viruses of Group A were recovered from four patients with obscure acute disease of the central nervous system and may have been the etiologic agents, an observation deserving of further pursuit.

Extraordinary persistence was finally rewarded by identification of Histoplasma capsulatum as the etiologic agent of an epidemic of an obscure type of pneumonia encountered in 1944 in an army camp. The retrospective account of the epidemic, the disability which ensued, the appearance of the typical miliary calcifications in the lungs all add confirmation to the recent elucidation of the natural history of the infection.

Contents continued on page 5

for results you can trust...

patients' reports you can rely on...

CLINITEST®

the urine-sugar test with the Laboratory Control

clear-cut color changes
in the clinically significant range

avoids trace reactions that confuse
the clinical picture

close correlation with quantitative tests

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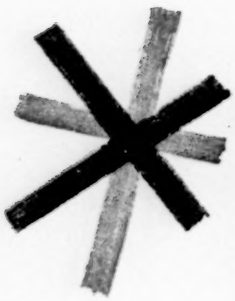

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CONTENTS continued–August 1956

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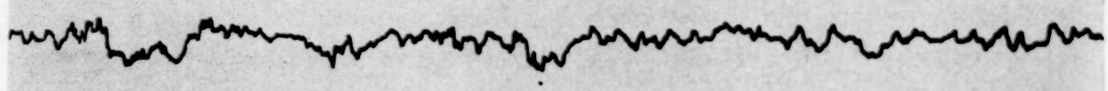
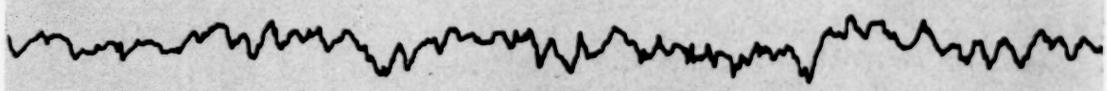
WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

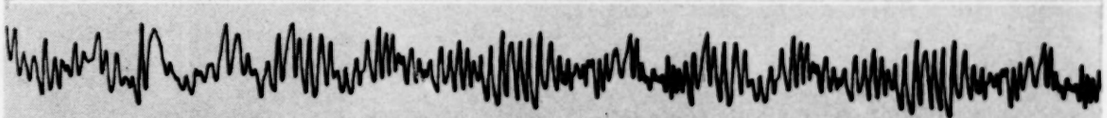
Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram



No drug.



After Raudixin. E. E. G. not altered.



After barbiturate. Typical "spindling" effect.

Because barbiturates and other sedatives depress the cerebral cortex, the sedation achieved is accompanied by a reduction in mental alertness.

Raudixin acts in the area of the midbrain and diencephalon, and does not depress the cerebral cortex. Consequently, the tranquilizing (ataractic) effect achieved is generally free of loss of alertness.

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Squibb Whole Root Rauwolfia Serpentina

DOSAGE: 100 mg. b.i.d. initially; may be adjusted within a range of 50 mg. to 500 mg. daily. Most patients can be adequately maintained on 100 mg. to 200 mg. per day.

SUPPLY: 50 mg. and 100 mg. tablets; bottles of 100, 1000 and 5000.

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Advertising Index on 3rd Cover

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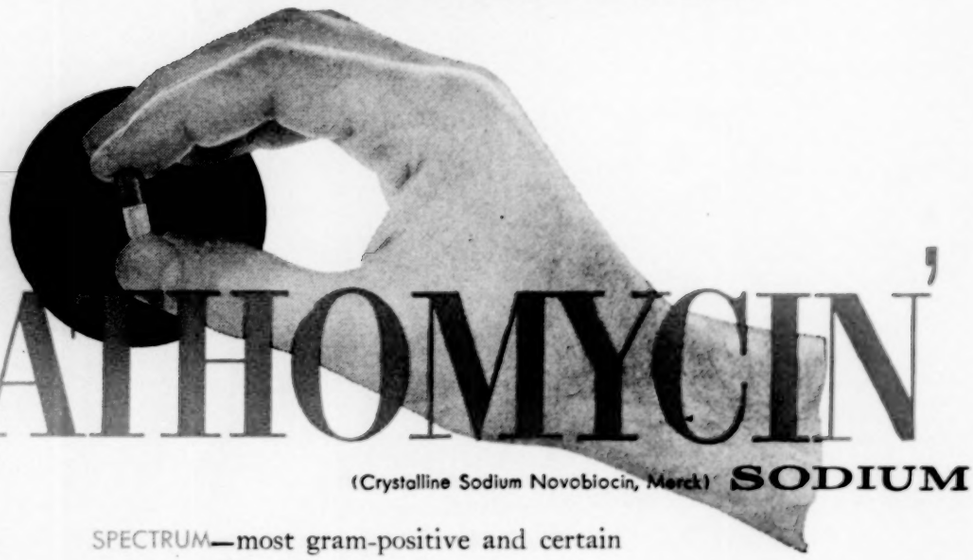
a unique new antibiotic of major importance

PROVED EFFECTIVE AGAINST SPECIFIC ORGANISMS
(staphylococci and proteus)

RESISTANT TO ALL OTHER ANTIMICROBIAL AGENTS



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SPECTRUM—most gram-positive and certain gram-negative pathogens.

ACTION—bactericidal in optimum concentration even to resistant strains.

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ABSORPTION—oral administration produces high and easily-maintained blood levels.

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DOSAGE—four capsules (one gram) initially and then two capsules (500 mg.) twice daily.

SUPPLIED—250 mg. capsules of 'CATHOMYCIN', bottles of 16.

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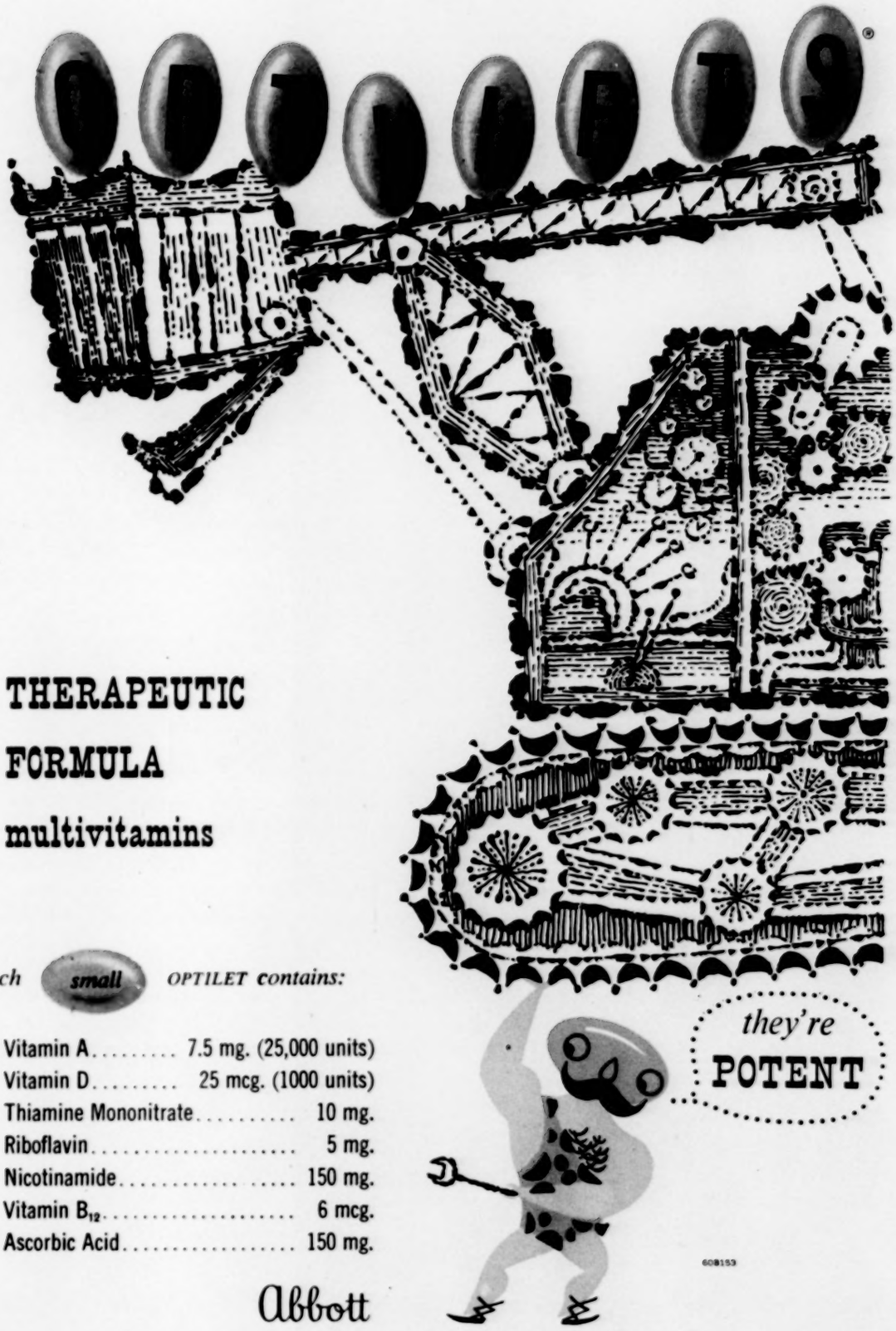

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orally effective muscle relaxant

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effective spasmolytic:

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1. Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

*T.M.
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Tetracycline *Lederle*

ACHROMYCIN is unsurpassed in its range of effectiveness. Each successive month more physicians are confirming this fact for themselves in their own daily practice in the therapy of respiratory, genitourinary, dermatologic and other infections.

ACHROMYCIN can be of service to you because of these important advantages:

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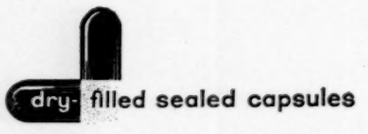
ACHROMYCIN Tetracycline with STRESS FORMULA VITAMINS for severe or prolonged illness. Attacks the infection – defends the patient – hastens normal recovery. Offered in Capsules of 250 mg. and in an Oral Suspension, 125 mg. per 5 cc. teaspoonful.



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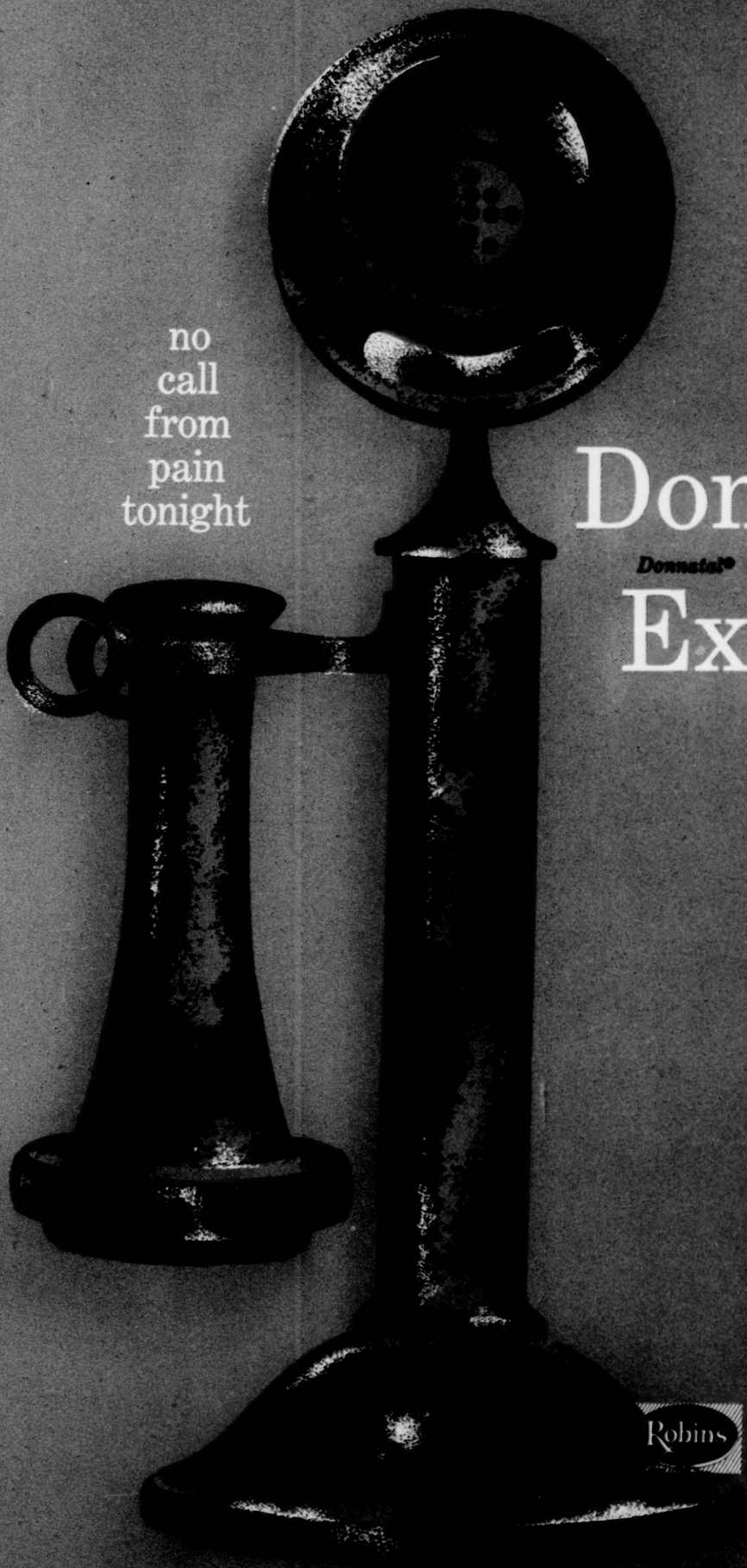

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NOW AVAILABLE...

a unique new antibiotic
of major importance
PROVED EFFECTIVE AGAINST
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(*staphylococci and proteus*)
RESISTANT TO ALL OTHER
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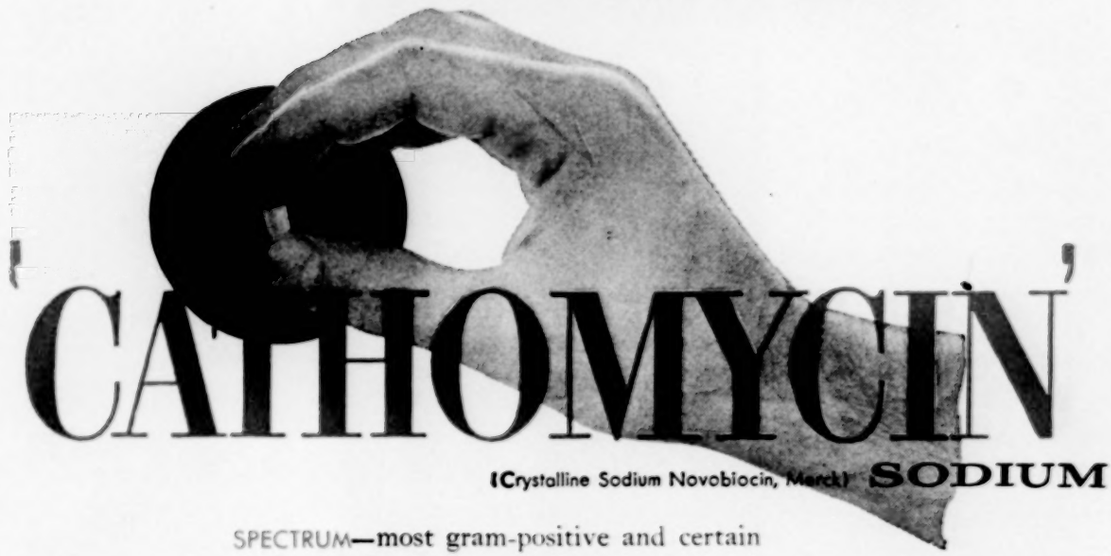

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SUPPLIED—250 mg. capsules of 'CATHOMYCIN', bottles of 16.

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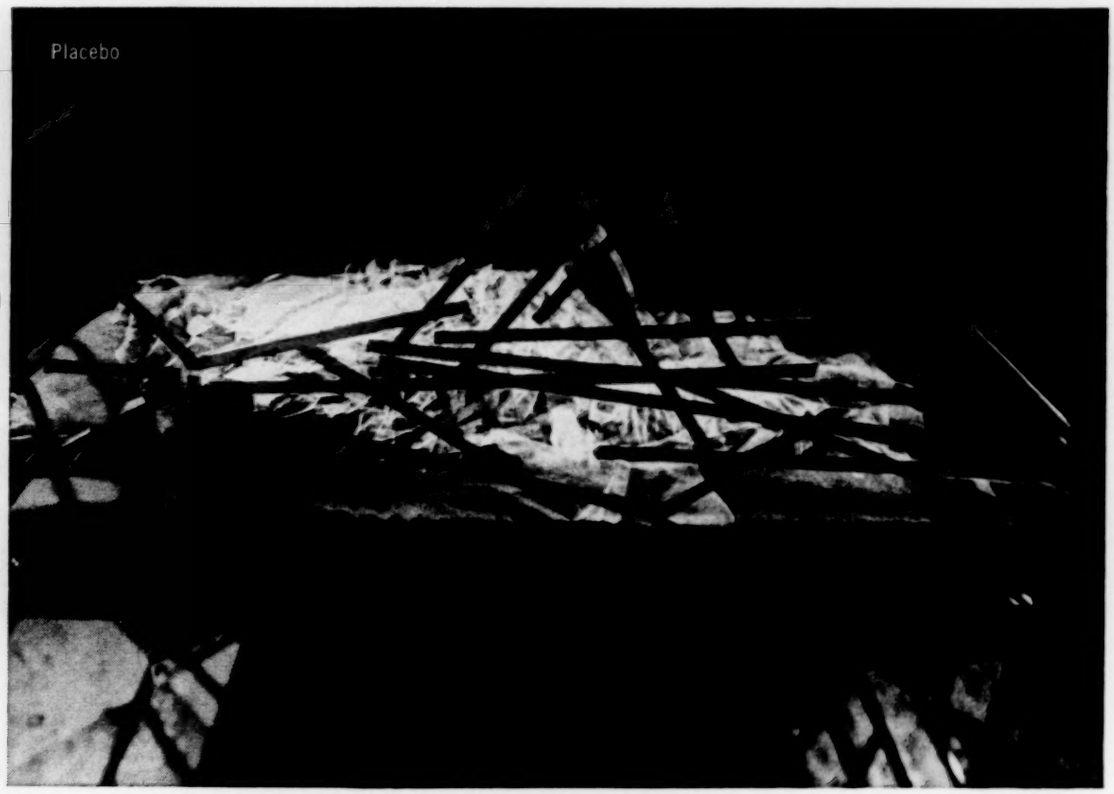
through-the-night photographs show...

NONBARBITURATE

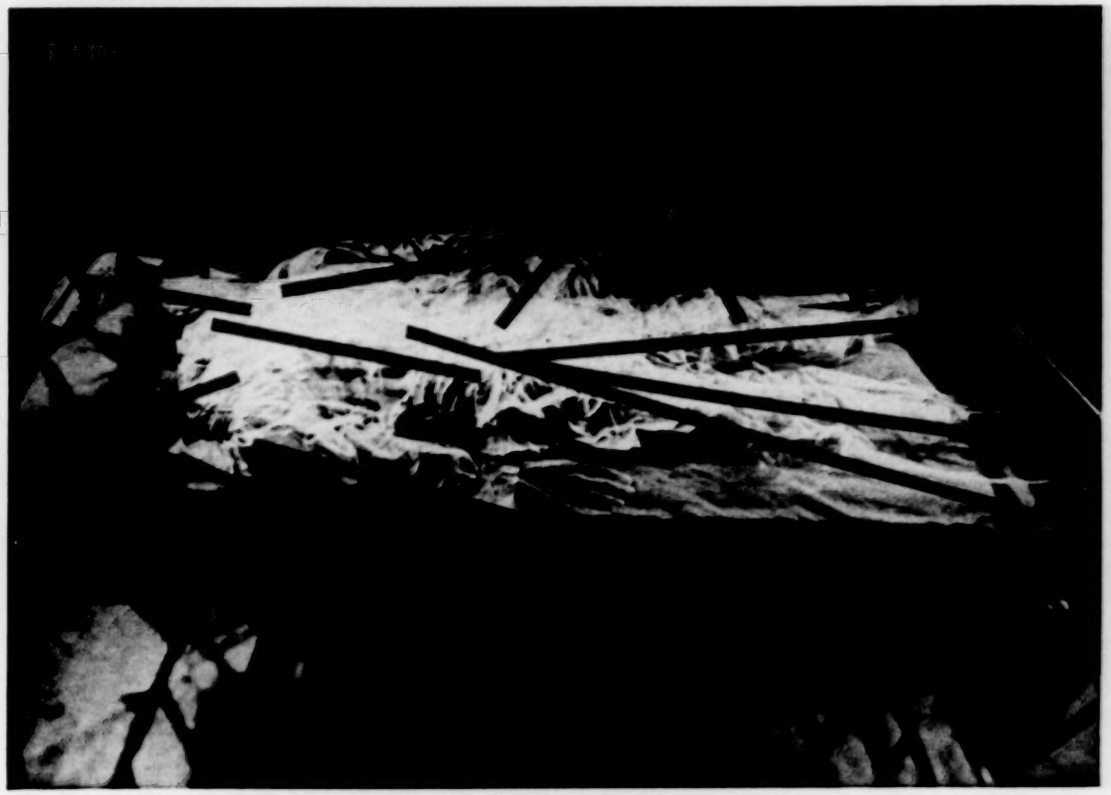
Doriden®



Twenty-eight-year-old male, restless sleeper, tense personality with occasional insomnia, was photographed at fixed intervals during the night to produce a series of exposures on same sheet of film. On placebo (above), unique "stroboscopic" picture shows him in typical fitful night of unrest.

Further clinical evidence of the sedative and hypnotic effectiveness of DORIDEN *is provided by numerous clinical studies. In most cases, Doriden acts in 15 to 30 minutes, affords 4 to 8 hours of refreshing sleep... and come morning, the patient awakens "clear-headed."*

induces sound, restful sleep



Same patient on successive night, following administration of Doriden 0.5 Gm. at bedtime, is shown in distinctly more restful repose. Total sleep was achieved in 16 minutes. Close study of activity pattern shows approximately 50 per cent reduction in overt motion and restlessness.

DORIDEN is also an excellent daytime sedative... calms the tense, anxious, overwrought patient.

DOSAGE: For SLEEP—0.5 Gm. at bedtime.
As a DAYTIME SEDATIVE—0.125 or 0.25 Gm. t.i.d. after meals.

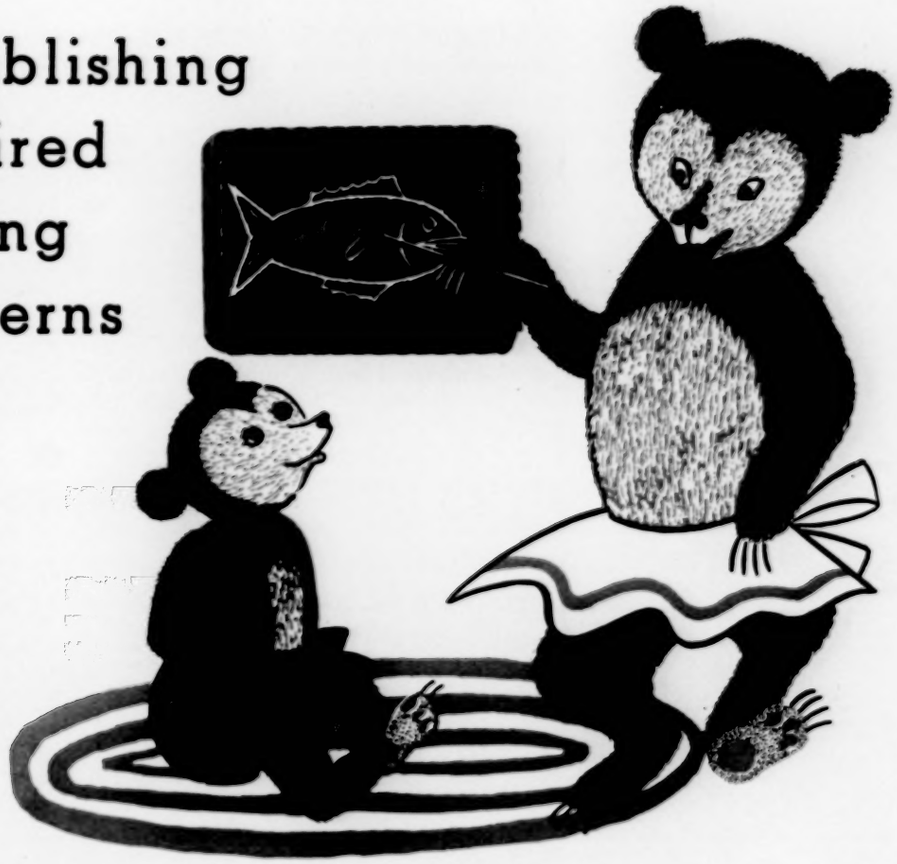
TABLETS, 0.125 Gm., 0.25 Gm. (scored) and 0.5 Gm. (scored).

DORIDEN® (glutethimide CIBA)

CIBA
SUMMIT, N. J.

2/22139M

establishing desired eating patterns



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and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

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to overcome specific infections that do not respond to any other antibiotic[1,2,3]....

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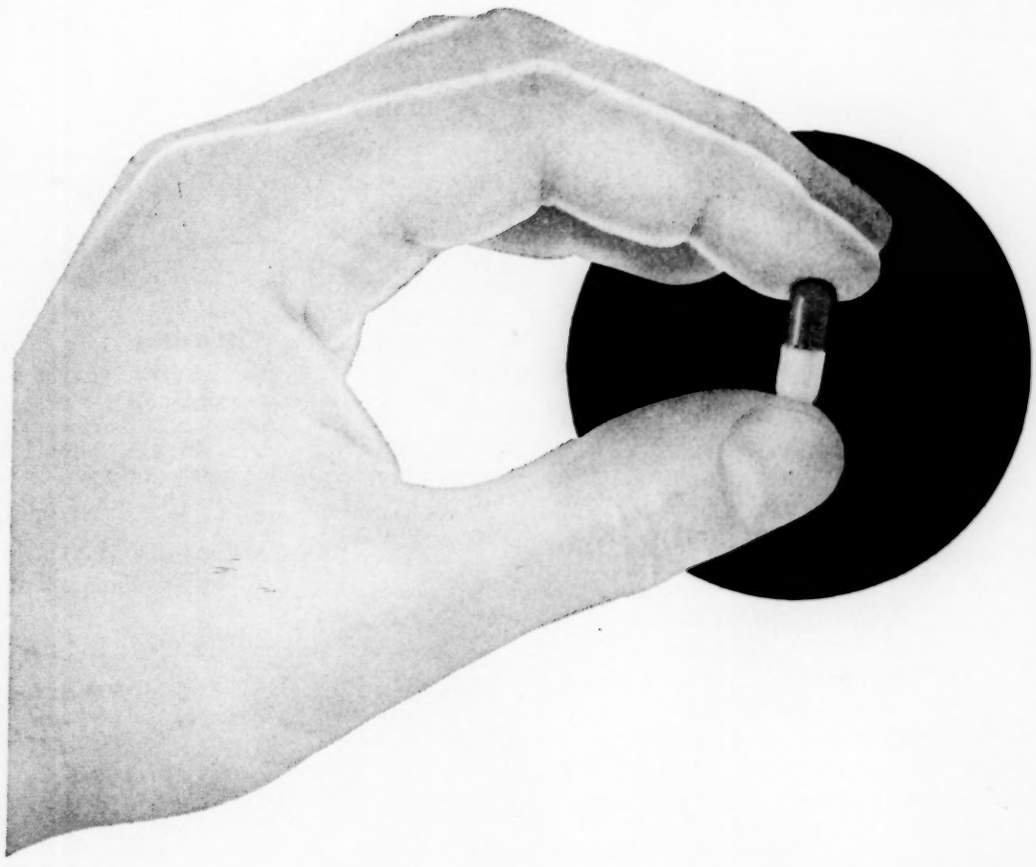

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SPECTRUM—'CATHOMYCIN' [1,2,3,5,6] has also been shown to be active against other organisms including—*D. pneumoniae*, *N. intracellularis*, *S. pyogenes*, *S. viridans* and *H. pertussis*, but clinical evidence must be further evaluated before 'CATHOMYCIN' can be recommended for these pathogens.

ACTION—'CATHOMYCIN' in optimum concentration is bactericidal. Cross-resistance with other antibiotics has not been observed.[7]

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ABSORPTION—'CATHOMYCIN' is readily absorbed, [5,6,9] and oral dosage produces significant blood and tissue levels which persist for at least 12 hours.[7]

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SUPPLIED: 'CATHOMYCIN' Sodium (Crystalline Sodium Novobiocin, Merck) in capsules of 250 mg., bottles of 16.

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better
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new broad-spectrum

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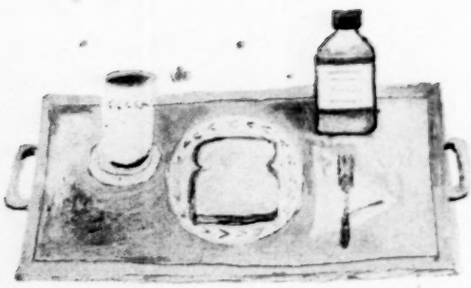
BRAND OF TETRACYCLINE



homogenized mixture

125 mg. tetracycline per 5 cc. teaspoonful. *Bottles of 2 fl. oz. and 1 pint, packaged ready to use.*

READY TO USE No reconstitution required.

READILY ACCEPTED Unusual, delicious fruit flavors.

RAPIDLY ABSORBED Fine particle dispersion—therapeutic blood levels within one hour.

RAPIDLY EFFECTIVE Fast, trouble-free tetracycline for control of the widest range of infections.

also available: vitamin-fortified **TETRABON SF†** (brand of tetracycline hydrochloride with vitamins) *homogenized mixture*: 125 mg. tetracycline per 5 cc. teaspoonful, plus vitamins of the B complex, C and K recommended for nutritional support in the stress of prolonged infection.

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Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

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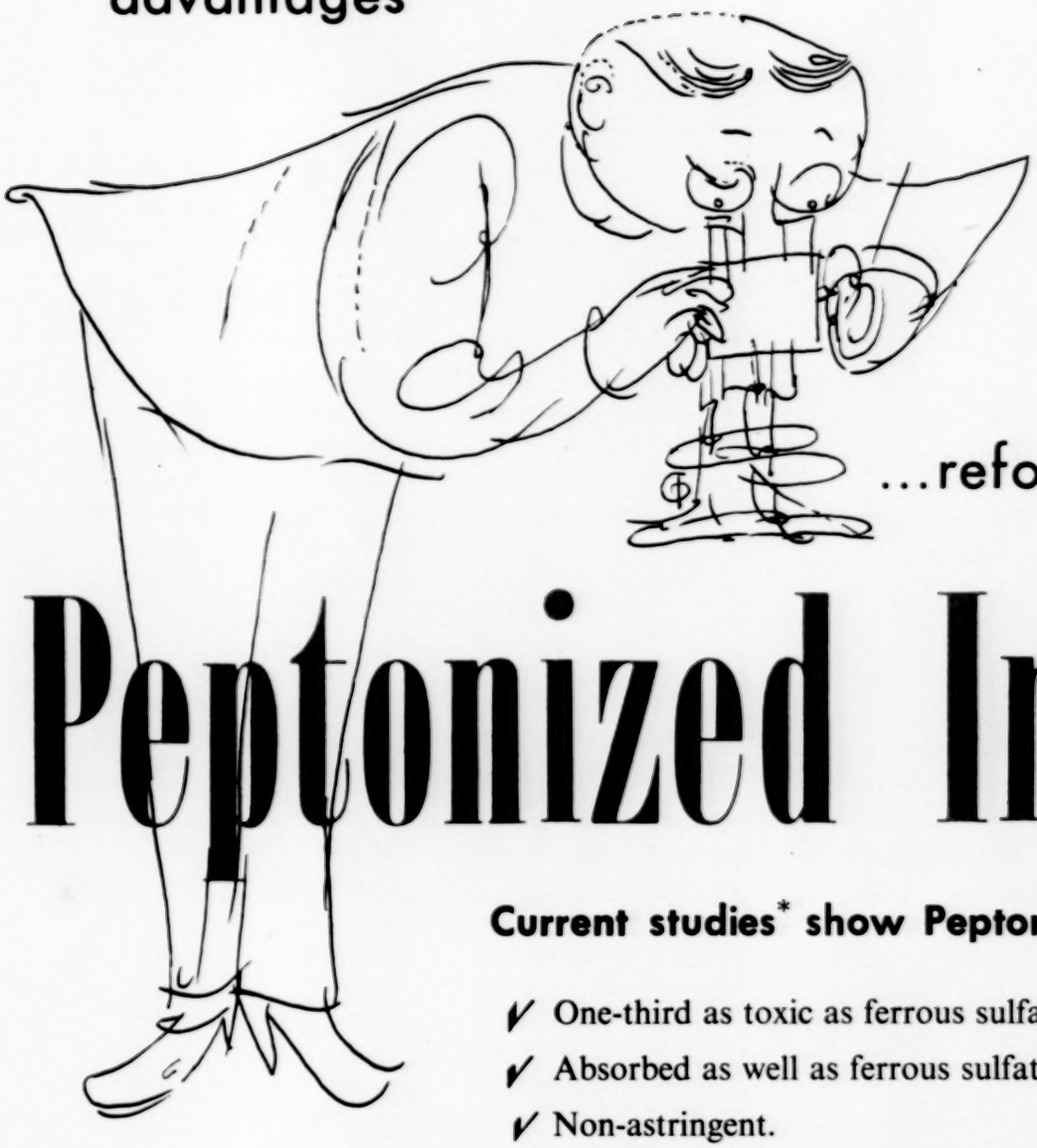

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- ✓ Free from tendencies to disturb digestion. (*One-tenth as irritating to the gastric mucosa as ferrous sulfate.*)
- ✓ More effective in iron-deficient anemias.

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*Keith, J. H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

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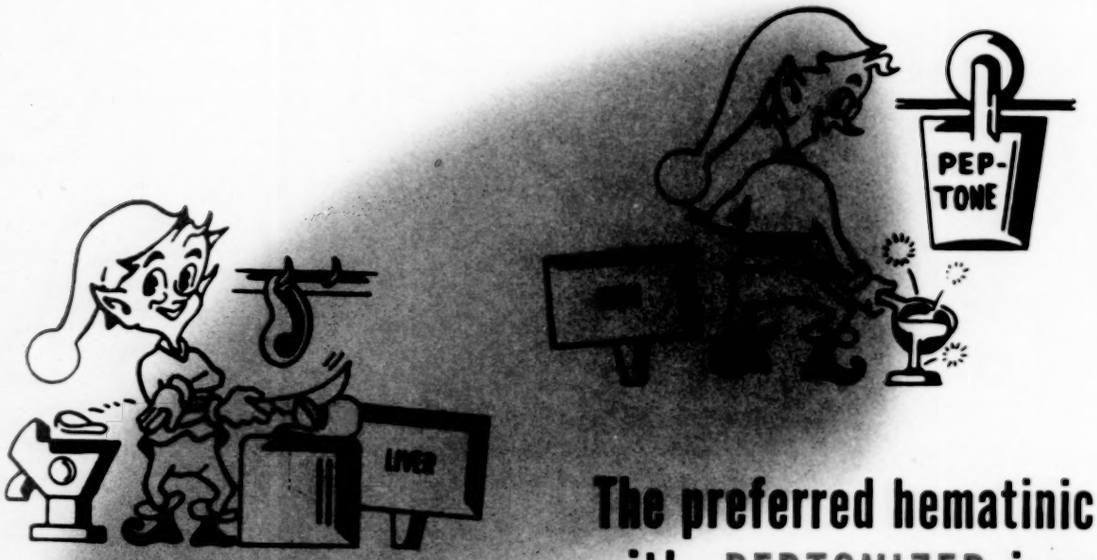

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Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

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Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York Kansas City San Francisco

THE MILTOWN MOLECULE

A tranquilizer well suited for prolonged therapy

NO ORGANIC CONTRAINDICATIONS

reported to date

- well tolerated, non-addictive, essentially non-toxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: anxiety and tension states, muscle spasm.

Miltown®

THE ORIGINAL MEPROBAMATE

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.

2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720

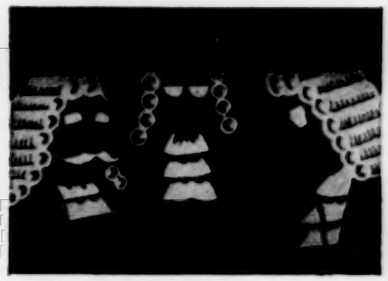
SUPPLIED: 400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.

Literature and Samples Available on Request

It's a date—

...among other things...which distinguishes Vi-Penta Drops 'Roche.' Since all multivitamin solutions tend to lose strength in time, Vi-Penta® Drops are dated to assure full label potency. Just 0.6 cc daily provides required amounts of A, C, D and B vitamins (including B_6), and you'll find that both mothers and youngsters like them because they're easy to give and easy to take... Hoffmann - La Roche Inc.

Nutley 10, N. J.



a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried .	0.12 Gm.
Calcium ascorbate	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
NEW YORK
KANSAS CITY
SAN FRANCISCO

The S. E. Massengill company

WEATHER OR NOT...

Nasal congestion is a year 'round problem
whether due to seasonal and perennial allergies,
sudden chills and rains of fall and spring,
or the severe ways of winter.
For quick relief . . . the collective advantages of
TYZINE represent the ideal in a nasal decongestant.

always time for

Tyzine®

brand of tetrahydrozoline hydrochloride

for relief of nasal congestion

in minutes for hours
(up to 6 hours with one dose)
. . . without rebound engorgement
. . . odorless, tasteless
. . . no sting, burn or irritation

supplied: TYZINE Nasal Solution, 1-oz. dropper bottles, 0.1%.
Nasal Spray, 15 cc., in plastic bottles, 0.1%.
Pediatric Nasal Drops, ½-oz. bottles, 0.05%,
with calibrated dropper for precise dosage.

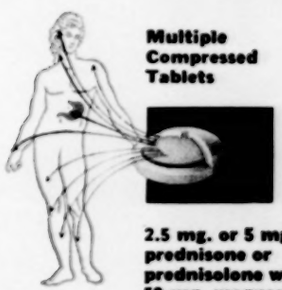
NOTE: *As with certain other widely used nasal decongestants, overdosage may cause drowsiness or deep sleep in infants and young children:* KEEP OUT OF HANDS OF CHILDREN OF ALL AGES. *TYZINE Nasal Spray and TYZINE Nasal Solution, 0.1%, are not recommended for use in children under six. When using TYZINE Nasal Spray in the plastic bottle, it should be administered only in an upright position.*

Pfizer PFIZER LABORATORIES DIVISION, CHAS. PFIZER & CO., INC. BROOKLYN 6, NEW YORK

ROUTINE CO-ADMINISTRATION MEANS

'Co-Hydeltra'

(Buffered Prednisolone)



Multiple Compressed Tablets

2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.

'Co-Deltra'

(Buffered Prednisone)

All the benefits of the "predni-steroids" plus positive antacid action to minimize gastric distress.

References: 1. Boland, E. W., *J.A.M.A.* **160**:613, (February 25,) 1956. 2. Margolis, H. M. *et al, J.A.M.A.* **158**:454, (June 11,) 1955. 3. Bollet, A. J. *et al, J.A.M.A.* **158**:459, (June 11,) 1955.

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

in bursitis, tendinitis, tenosynovitis

DRAMATIC RELIEF OF PAIN AND DISABILITY

MY-B-DEN®

(adenosine-5-monophosphate)

Bischoff DIVISION

pain is relieved... function returns...
swelling subsides... residual tenderness disappears

this is the response pattern in acute and subacute bursitis with only 7 or 8 injections.[1] An average of 9 injections in chronic calcified tendinitis produces "unusually good results."[2]

Literature available to physicians—write Medical Service Department.

references: (1) Rottino, A.: Journal-Lancet *71*:237, 1951. (2) Susinno, A. M., and Verdon, R. E.: J.A.M.A. *154*:239 (Jan. 16), 1954.

AMES COMPANY, INC · ELKHART, INDIANA

10584

1 in 1 tablet

bacterial + symptomatic

control of Urinary Infections

Your patients on Azo Gantrisin soon feel and even see the prompt action of the analgesic dye as it soothes the inflamed urogenital mucosa and colors the urine orange-red.

Gantrisin, the single, wide-spectrum sulfonamide, promptly achieves effective plasma and urine levels, attacking pathogens both systemically and locally.

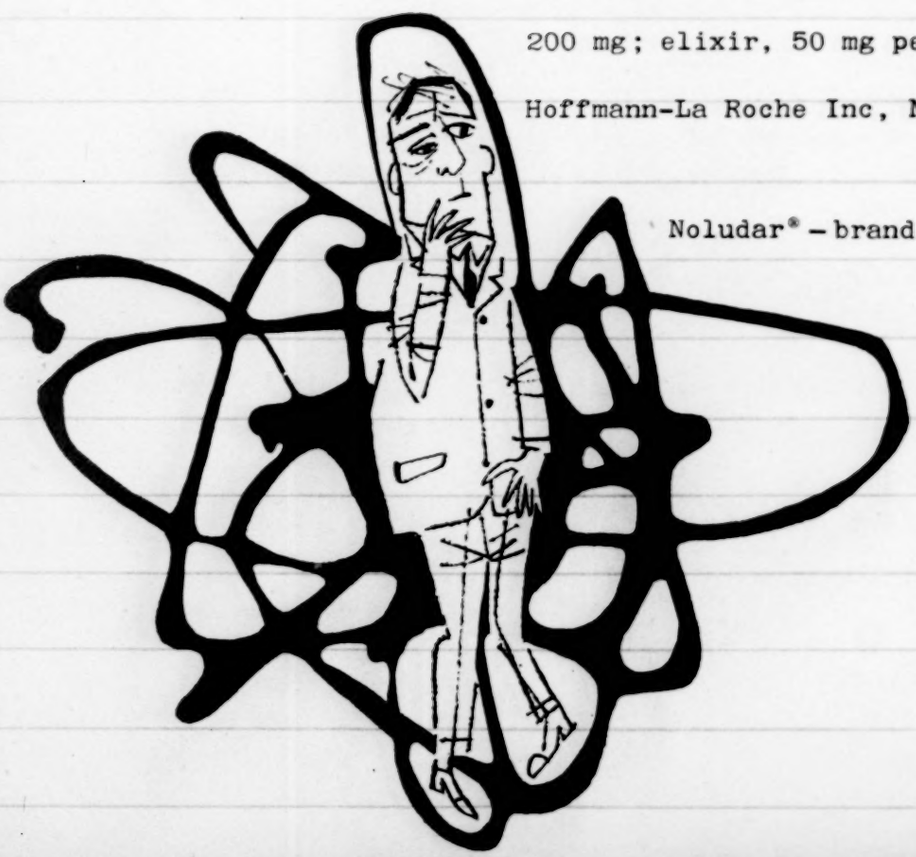
Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin® - brand of sulfisoxazole, and 50 mg phenylazo-diamino-pyridine HCl.

'Roche' | Original Research in Medicine and Chemistry

For patients wound up in a tangle of nerves—

Noludar 'Roche' provides relaxation. Not a barbiturate, not habit forming, 50 mg t.i.d. brings daytime sedation without undue drowsiness, while 200 mg h.s. usually induces a restful night's sleep with a clear-headed awakening. Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoonful.

Hoffmann-La Roche Inc, Nutley, N.J.

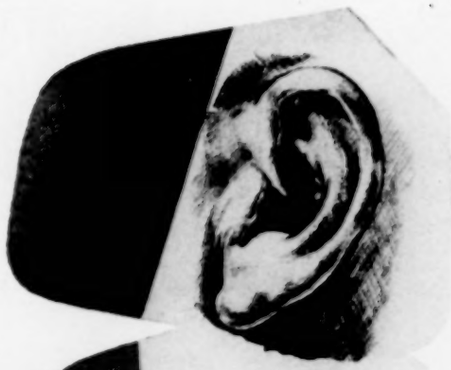


Noludar® – brand of methyprylon

for superficial bacterial infections of the skin and external ear

Spectrocin Ointment

Squibb Neomycin-Gramicidin in Plastibase*
15 and 30 gram tubes



for superficial bacterial infections of the eye

Spectrocin Ophthalmic Ointment

Squibb Neomycin-Gramicidin in Plastibase*
3.6 gram ophthalmic tubes

for symptomatic relief of minor throat irritations

Spectrocin-T

Squibb Neomycin-Gramicidin-Benzocaine Troches
boxes of 10 and bottles of 48

The organisms responsible for most superficial bacterial infections are highly susceptible to neomycin; those which are only slightly susceptible or resistant to neomycin are usually susceptible to gramicidin.

Neomycin is rarely administered systemically, and gramicidin never. With Spectrocin (Squibb Neomycin-Gramicidin), therefore, there is no danger of sensitizing patients to antibiotics generally used systemically for serious infections.

SQUIBB *Squibb Quality—the Priceless Ingredient*

*(SQUIBB OLEAGINOUS OINTMENT BASE)

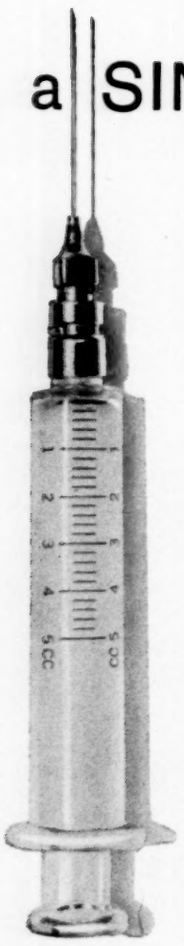
SP-56

treat adrenocortical insufficiency

without the
difficulties
of
implants

without the
unpleasantness
of daily
injections

with a SINGLE injection a month



Percorten®

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

Percorten trimethylacetate, developed after more than 3 years of research by CIBA, provides expedient, lasting hormonal support for the patient with adrenocortical hypofunction . . . avoiding both the uncertainty of surgical implantation and the vexation of daily injections. With once-a-month therapy, a single injection will produce prolonged activity without acute signs of overdosage.[1]

Multiple-dose Vials, 4 ml., containing 25 mg. Percorten trimethylacetate per ml. as an aqueous microcrystalline suspension for intramuscular use only.

1. Frawley, T. F., and Forsham, P. H.: J. Clin. Endocrinol. *11*:772 (July) 1951.

CIBA
SUMMIT, N. J.

you'd never know he has a peptic ulcer

he's symptom free...

day after day after day...

week after week after week

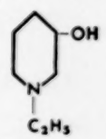
cholinolytic

PIPTAL®

- normacid gastric action
- normalizes G.I. tonus and motility
- prolongs remissions, curbs recurrences
- virtually free from "anticholinergic" side effects

One tablet t.i.d. before meals and 1 or 2 tablets at bedtime. PIPTAL is the *only* brand of N-ethyl-3-piperidyl-benzilate methobromide.

LAKESIDE



00956

IN WOMEN,

the preferred broad spectrum antibiotic preparation is

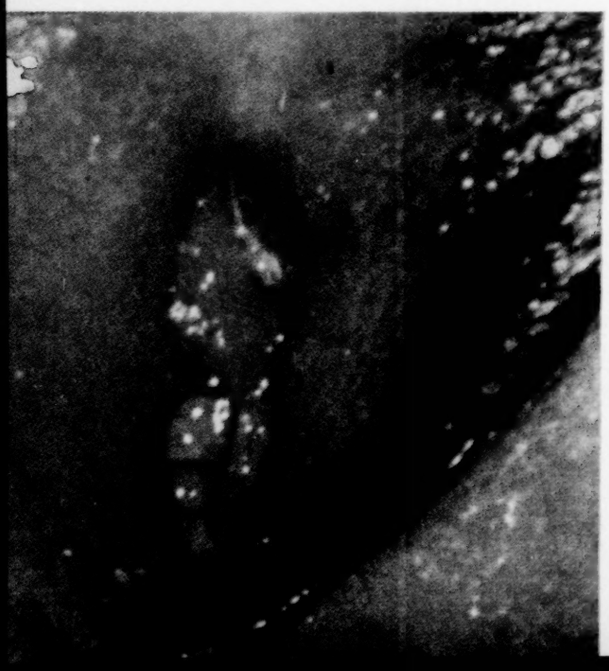
MYSTECLIN

STECLIN-MYCOSTATIN (SQUIBB TETRACYCLINE-NYSTATIN)

Usual broad spectrum antibiotic therapy may be followed by vaginal moniliasis. Mysteclin supplies well tolerated broad spectrum therapy without subsequent vaginal moniliasis.*

*Stone, M. L., and Mersheimer, W. L.: "Comparison of side effects of tetracycline and tetracycline combined with nystatin." Antibiotics Annual 1955-56, New York, Medical Encyclopedia Inc., 1956, p. 862.

Vaginal moniliasis following antibiotic therapy



Oral antibiotic therapy may cause an overgrowth of monilia in the vagina, producing vaginal moniliasis with vulvar pruritus and vaginal discharge. All women are susceptible, but this complication is especially frequent in women who are pregnant or diabetic. In many cases, the woman fails to inform the physician through embarrassment or failure to relate the condition to preceding antibiotic therapy.

SQUIBB

vaginal moniliasis: an increasingly common complication of antibiotic therapy

"... wide use of penicillin and broad spectrum antibiotics, with resultant disturbance of vaginal bacteriology has increased markedly the incidence of yeast and fungus infections of the vagina.... Before advent of the wonder drugs, relationship of trichomonas to monilia was roughly four to one in the usual office practice. Within the past eight years the ratio has been reversed with three monilia problems to one of trichomonas."

Lee, A. F. and Keifer, W. S.:
Northwest Med. 53:1227 (Dec.) 1954.

"Vaginal moniliasis . . . is quite common and the incidence may well have been increased following the extensive use of the broad-spectrum drugs or prolonged oral use of penicillin."

Welch, H.: Editorial,
Antibiotic Med. 2:79 (Feb.) 1956.

MYSTECLIN

the only broad spectrum antibiotic preparation that:

1: provides the antibacterial activity of tetracycline and

2: protects the patient against monilial superinfection

Each Mysteclin capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride, a well tolerated broad spectrum antibiotic, and 250,000 units Mycostatin (Squibb Nystatin), the first well tolerated antibiotic active against fungi. Minimum adult dosage: 1 capsule q.i.d. Supply: Bottles of 16 and 100.

also available: MYSTECLIN Half Strength Capsules (125 mg. Steclin Hydrochloride and 125,000 units Mycostatin): Bottles of 16 and 100.

A PARTIAL LIST OF INDICATIONS FOR MYSTECLIN

When caused by tetracycline-susceptible organisms, the following conditions are among those which may be expected to respond to Mysteclin:

- Abscess
- Bronchiectasis
- Bronchitis
- Bronchopneumonia
- Burns, Infected
- Cellulitis
- Cervicitis
- Chancroid
- Colitis
- Cystitis
- Diarrheas, Infectious
- Dysentery, Amebic
- Dysentery, Bacillary
- Empyema
- Endocarditis, Bacterial
- Epididymitis
- Furunculosis
- Gastroenteritis
- Gonorrhea
- Granuloma Inguinale
- Klebsiella Pneumonia
- Laryngitis
- Lymphadenitis
- Lymphangitis
- Lymphogranuloma Venereum
- Mastoiditis
- Meningitis
- Metritis
- Osteomyelitis
- Otitis Media
- Peritonitis
- Pertussis
- Pharyngitis
- Pneumonia
- Psittacosis
- Pyelonephritis
- Q Fever
- Rocky Mountain Spotted Fever
- Salpingitis
- Scarlet Fever
- Scrub Typhus
- Sepsis, Puerperal
- Septic Sore Throat
- Septicemia
- Sinusitis
- Skin Graft Infections
- Surgical Prophylaxis
- Tonsillitis
- Tracheobronchitis
- Tularemia
- Typhus
- Urethritis
- Vesiculitis
- Wounds, Infected

It is impossible to predict with certainty in which patients clinical moniliasis may develop as a result of broad spectrum antibiotic therapy.

However, the added protection afforded by Mysteclin against monilial superinfection is *especially* important when antibiotic therapy must be prescribed in high dosage or for prolonged periods.

It is also particularly important in women; in debilitated, elderly, or diabetic patients; in infants (particularly prematures); in patients for whom concomitant cortisone or related steroid therapy is prescribed; and in individuals who have developed a monilial complication on previous broad spectrum therapy.

"MYSOLINE" effectively controls grand mal and psychomotor seizures

Control of seizures was obtained in 57 per cent of 97 grand mal patients where "MYSOLINE" was used as initial therapy; an additional 22 per cent were improved.[1] In patients refractory to previous standard medication, Pence[2] obtained improvement to complete control in 70 per cent of cases. In his study, "MYSOLINE" was added to current medication and in some cases this was replaced by "MYSOLINE" alone. He observed that patients can usually remain under control without necessitating dosage increases above the established maintenance level. "Grand mal convulsions, psychomotor automatisms and focal motor convulsive disorders respond most readily to this drug."[3]

NOTABLY FREE FROM SERIOUS TOXIC EFFECTS

Urinalyses and blood counts during therapy failed to reveal any abnormalities.[2] When side reactions do occur, they are usually mild and transient and tend to disappear as therapy is continued.

"MYSOLINE"®

Brand of Primidone

in epilepsy

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

LITERATURE ON REQUEST

1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

Ayerst Laboratories • New York, N.Y. • Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical (Pharmaceuticals) Limited.

5656

HOMAGENETS®*

The homogenized vitamins

Homagenets supply vitamins in the same way as do the most nutritious foods. In this new dosage form, the vitamins are homogenized, then fused into a solid tablet. Because they are minutely subdivided, the vitamins are absorbed and utilized much more efficiently.

- *Better absorption, better utilization*
- *Excess vitamin dosage unnecessary*
- *Pleasant, candy-like flavor*
- *No regurgitation, no "fishy burp"*
- *May be chewed, swallowed or dissolved in the mouth*

Three formulas: Prenatal, Pediatric, Therapeutic

Samples available on request

*U.S. Pat. 2676136

THE S. E. MASSENGILL COMPANY • Bristol, Tennessee • New York • Kansas City • San Francisco

New ganglionic blocker lowers blood pressure consistently, predictably, usually with just 2 oral doses per day

Patients with moderate to severe essential hypertension, and even with malignant hypertension, often respond satisfactorily to a ganglionic blocking agent such as Ecolid. It can be used alone or — for maximal control of blood pressure with minimal side effects — in combination with other antihypertensive agents such as Serpasil or Apresoline.

Advantages

Ecolid has the following advantages over other ganglionic blockers:

- long action, usually requires only two oral doses per day
- rapid absorption — promptly reduces systolic and diastolic pressures
- consistent and predictable response — smoother control
- lower dosage required than with other ganglionic blockers
- minimal likelihood of drug tolerance

Clinical observations

In a study of four ganglionic blocking agents, Winsor[1] found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson[2] reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.[2,3]

For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."

References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

SUPPLIED: ECOLID Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).

DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

Ambulatory patients		
DAY	A.M.	P.M.
1	25 mg.	—
2	25 mg.	25 mg.
3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

Hospitalized patients		
DAY	A.M.	P.M.
1	50 mg.	—
2	50 mg.	50 mg.
3	100 mg.	50 mg.
4	100 mg.	100 mg.

to optimal response

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ROTOCOTES T.M. (dry-compressed, coated tablets CIBA)

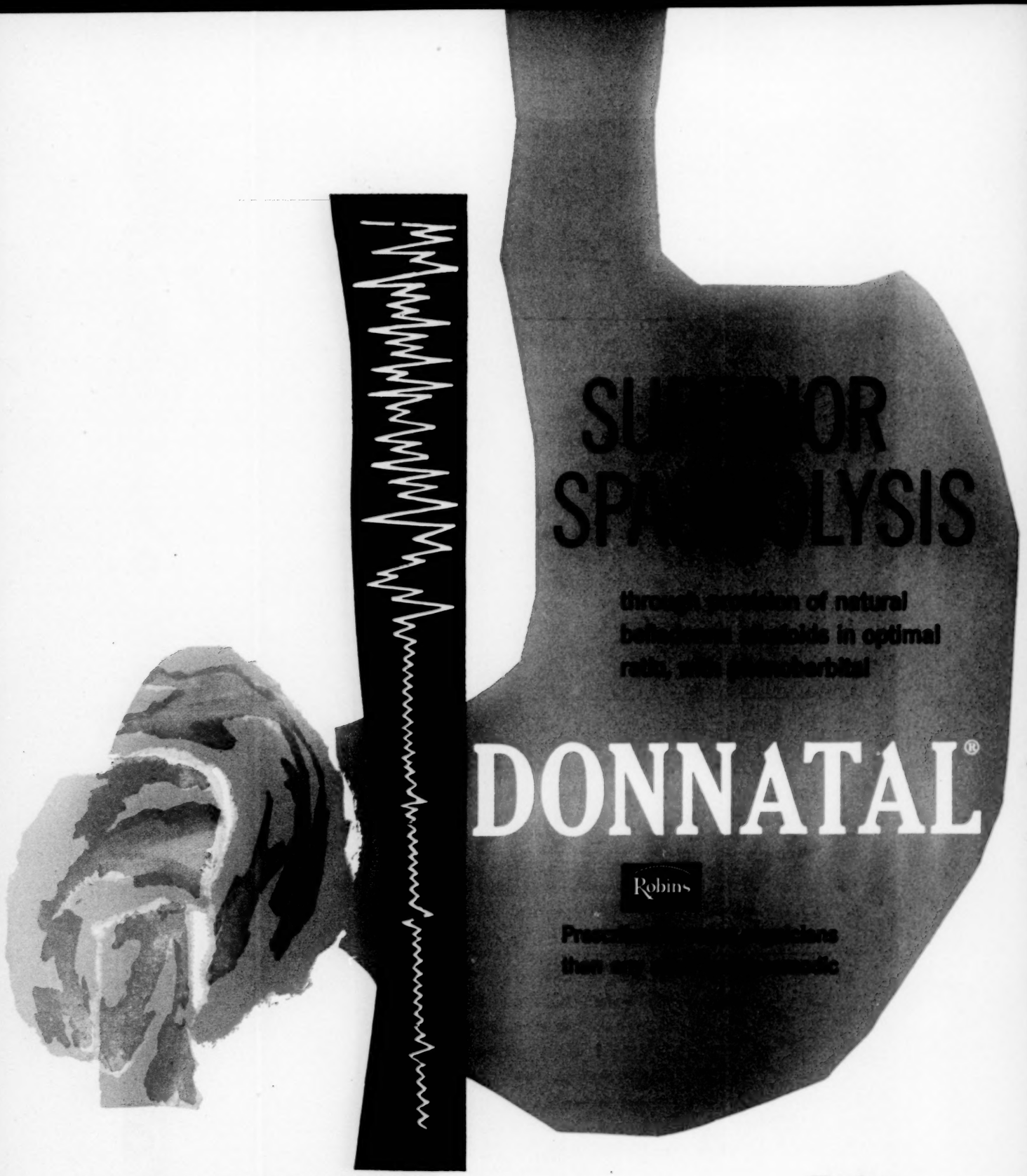
Ecolid T.M.
chloride
(chlorisondamine chloride CIBA)

REPRESENTATIVE CLINICAL STUDIES OF **Ecolid***

Number of Patients	Initial Oral Dosage	Responses	Duration of Action	References
		[illegible] other ganglionic [illegible], small doses of Ecolid were employed and greater hypotensive effect was obtained. Rapid absorption and long duration of hypotensive action.	Postural hypotension lasted 13.4 hours in 5 "test" patients receiving doses of 150 mg.	1
		Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
		Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
		25 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
		Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

[illegible] a total of 55 [illegible] patients [illegible]
[illegible] than 500 patients. They [illegible]
[illegible] was high [illegible]
[illegible] of action about [illegible]
[illegible] supine pressure in most cases.

**Information not available.



A. H. ROBINS CO., INC., RICHMOND 20, VA.
Ethical Pharmaceuticals of Merit since 1878

Robins

FORMULA

Donnatal Tablets
Donnatal Capsules
Donnatal Elixir (per 5 cc.)

Hyoscyamine Sulfate	0.1037 mg.
Atropine Sulfate	0.0194 mg.
Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

DONNATAL® EXTENTABS®
(Extended Action Tablets)

Each Extentab (equivalent to 3 Tablets) provides sustained 1-tablet effects... evenly, for 10 to 12 hours—all day or all night on a single dose.

Also available without phenobarbital component, as **Donna® Extentabs®**.

Hypotensive action without side effects

RENIR

Reserpine with a safety factor

The desirable hypotensive action of reserpine is often accompanied by distressing side effects. These include nasal congestion, hyperperistalsis, nightmares and mental depression.

Renir, which provides the desired action of reserpine, counterbalanced by the well-known effects of ephedrine, offers the optimum in hypotensive therapy. Untoward reactions are minimized, and tranquilization is maintained.

Investigators state that: ". . . with reserpine and ephedrine, the untoward effects of each are counteracted and the desirable effects of each are enhanced."[1]

INDICATIONS: In the treatment of mild, moderate and labile hypertension. Also anxiety and tension states; mild to severe neurosis.

SUGGESTED DOSAGE: For hypertension, 1 to 3 tablets daily. As a tranquilizer in mentally disturbed states, 2 to 4 tablets daily.

SUPPLIED: Tablets containing reserpine 0.25 mg., and ephedrine 8.0 mg., in bottles of 100.

CONTRAINDICATIONS: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

LITERATURE AND SAMPLES ON REQUEST.

1. *Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, A Superior Hypotensive-Tranquilizer. In press.*

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York • Kansas City • San Francisco

quicker relief
and shortened disability
in Herpes Zoster and Neuritis

Protamide®

... Five Year Clinical Evaluation

With only one to four injections of Protamide® prompt and complete recovery was obtained in 84% of all herpes zoster patients and in 96% of all neuritis patients treated during a five-year period by Drs. Henry W., Henry G., and David R. Lehrer (Northwest Med. 75:1249, 1955).

The investigators report on a total of 109 cases of herpes zoster and 313 cases of neuritis, all of whom were seen in private practice. All but one patient in each category responded with complete recovery.

This significant response is attributed to the fact that Protamide therapy was started promptly at the patient's first visit.

The shortening of the period of disability by this method of management is described as "a very gratifying experience for both the physician and the patient."

Protamide® is a sterile colloidal solution prepared from animal gastric mucosa ... free from protein reaction ... virtually painless on administration ... used intramuscularly only. Available from supply houses and pharmacies in boxes of ten 1.3 cc. ampuls.

Protamide®

... a product of *Sherman Laboratories*
Detroit 11, Michigan

Protamide®

megaloblastic anemia

one of the many anemias which can be effectively treated with

PERIHEMIN*

Hematinic Lederle

Nine out of 10 of all treatable anemias respond to PERIHEMIN. Its potent formula includes every known hemopoietic agent, including Purified Intrinsic Factor Concentrate. With this single product, you provide complete anemia therapy in a form convenient for the patient.

Dosage: one capsule, t.i.d.

Each capsule contains:

Vitamin B_{12} with Intrinsic Factor Concentrate	½ U.S.P. Oral Unit
Vitamin B_{12} (additional)	5 mcgm.
Ferrous Sulfate (Exsiccated)	192 mg.
Folic Acid	0.85 mg.
Ascorbic Acid (C)	50 mg.
Insoluble Liver Fraction	50 mg.

PERIHEMIN JR *Capsules*, for children, are approximately one-quarter the potency of this formula.

dry filled sealed capsules (a Lederle exclusive!) for more rapid and complete absorption!

LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

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References: 1. Gamble, J.R., et al. Arch. Int. Med. **95**:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. **42**:805, 1953.

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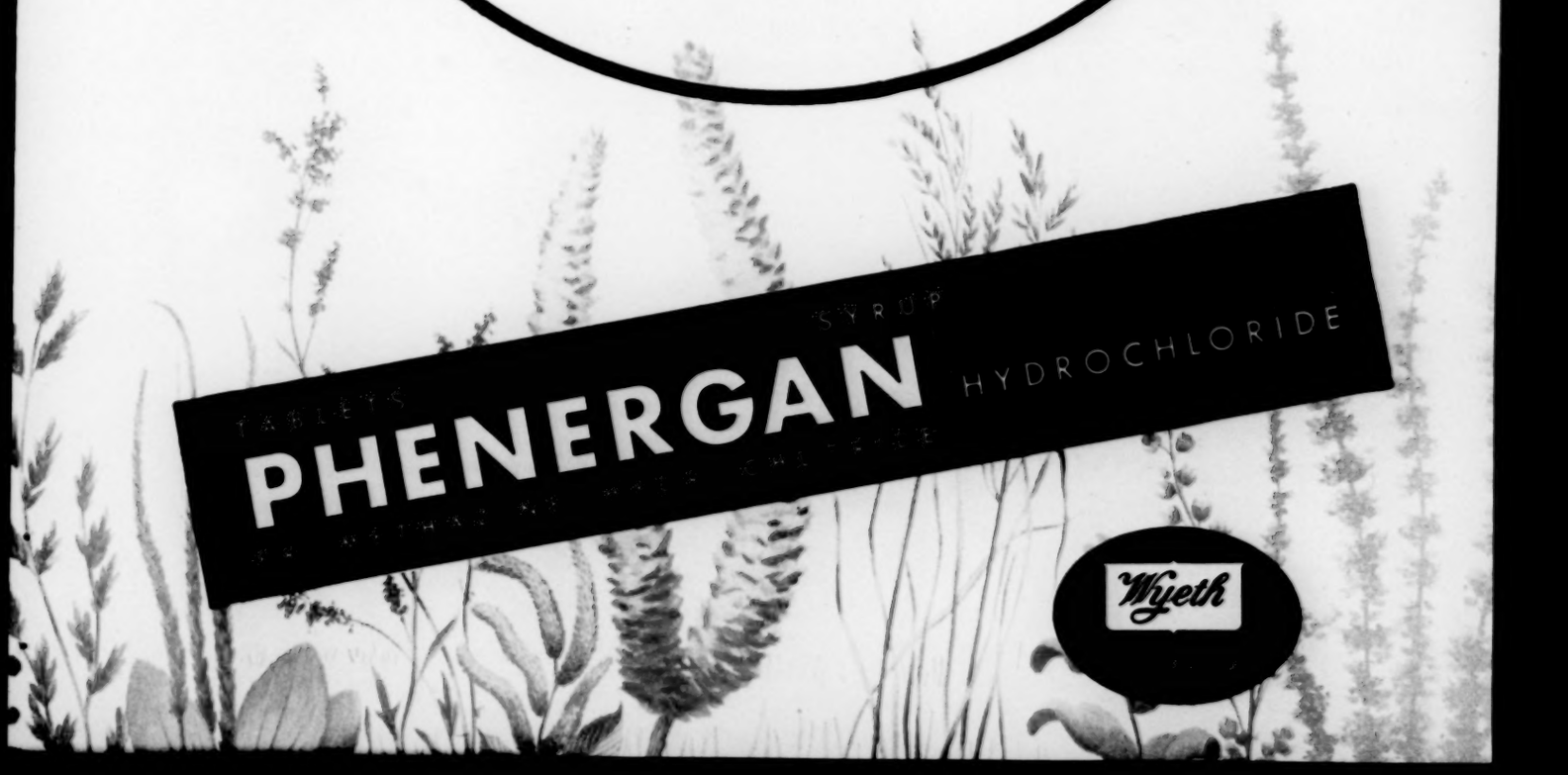

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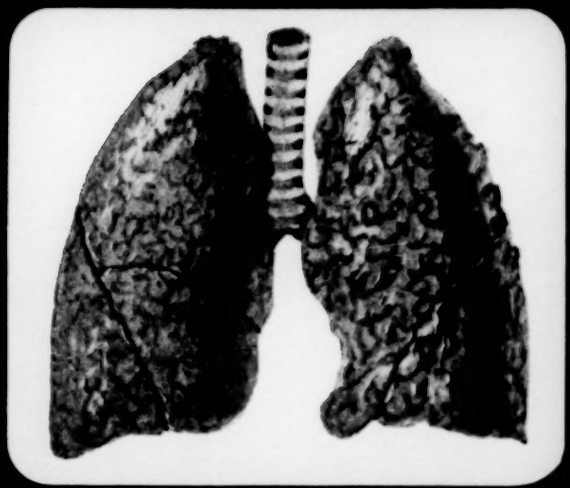

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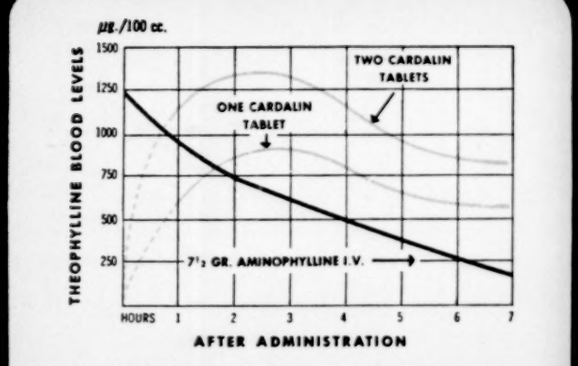
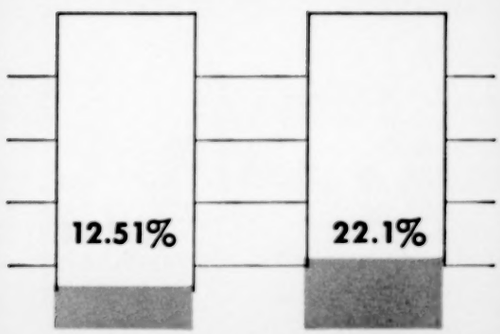


(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)



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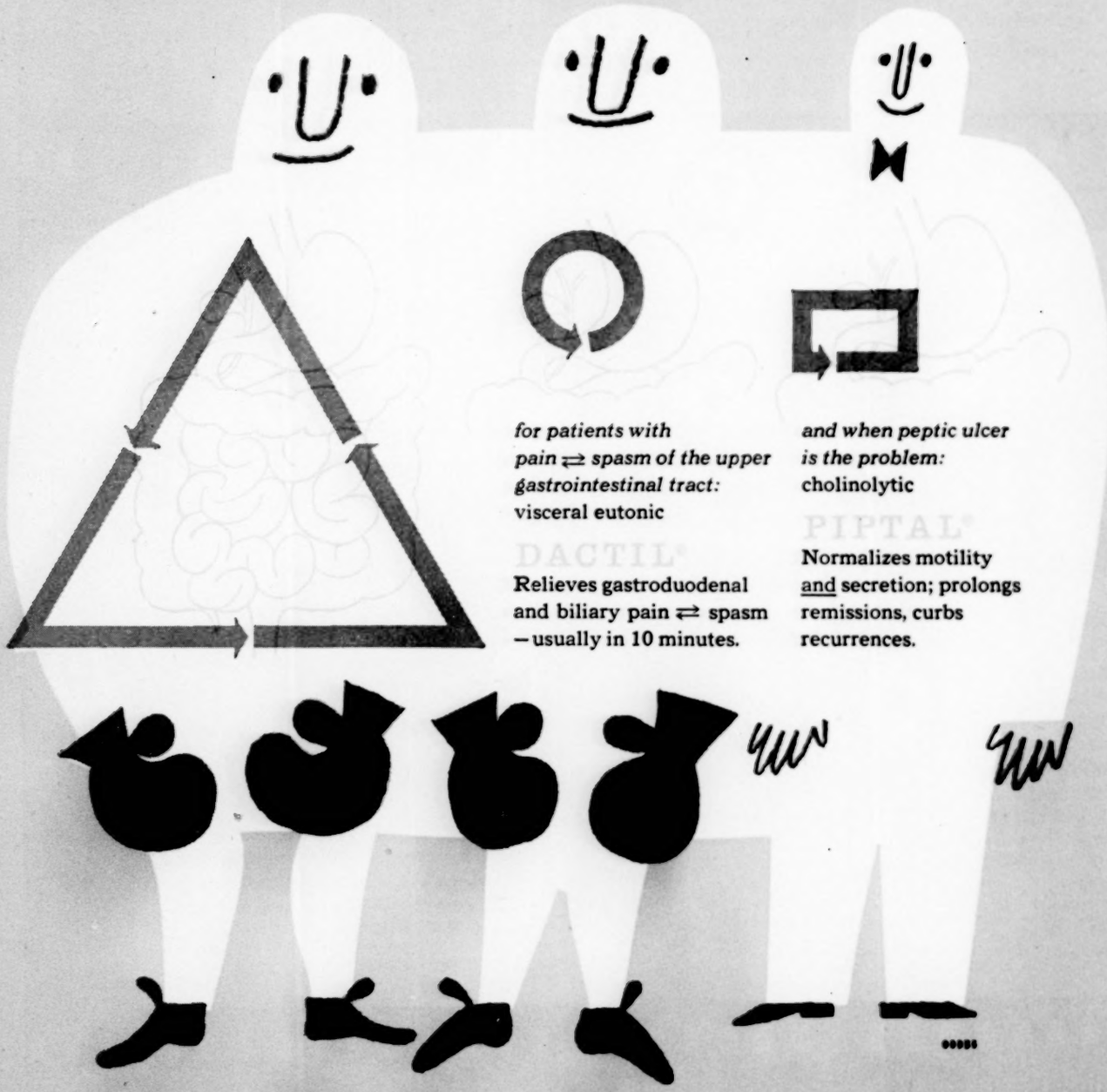

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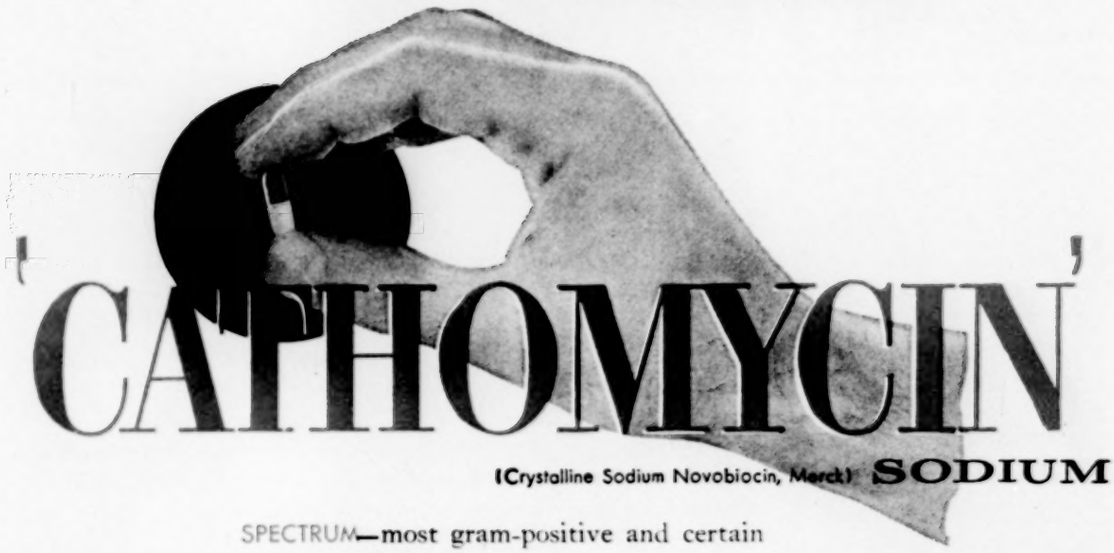

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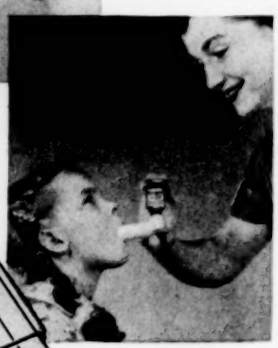

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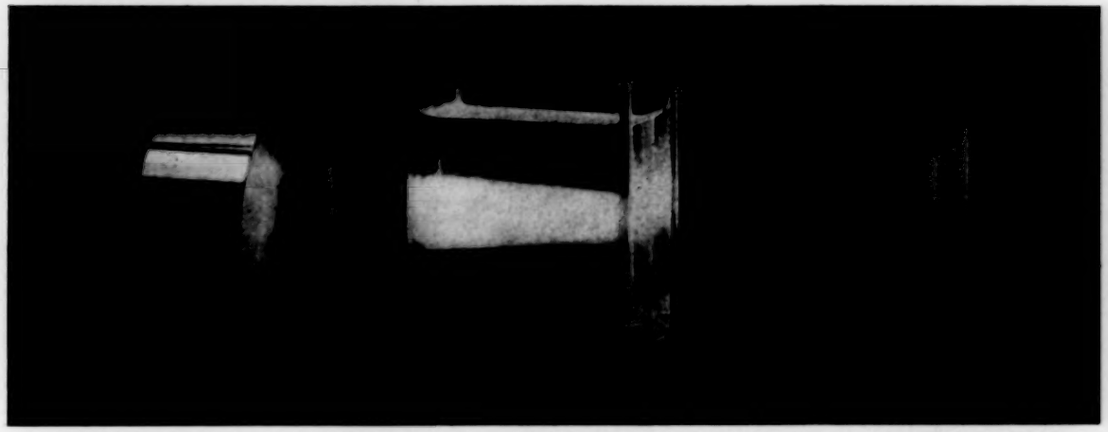

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Bibliography: 1. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, The Macmillan Company, 1952, p. 184. • 2. Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, p. 64/6. • 3. Ahrens, E. H., Jr., and Kunkel, H. G.: J. Exper. Med. *90*:409 (Nov. 1) 1949.

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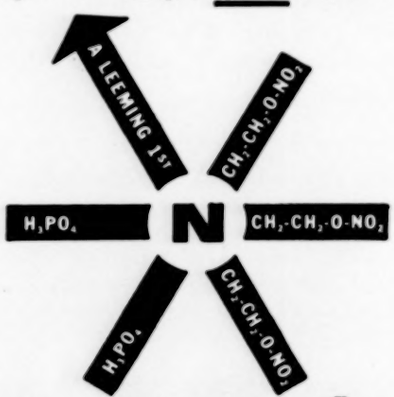

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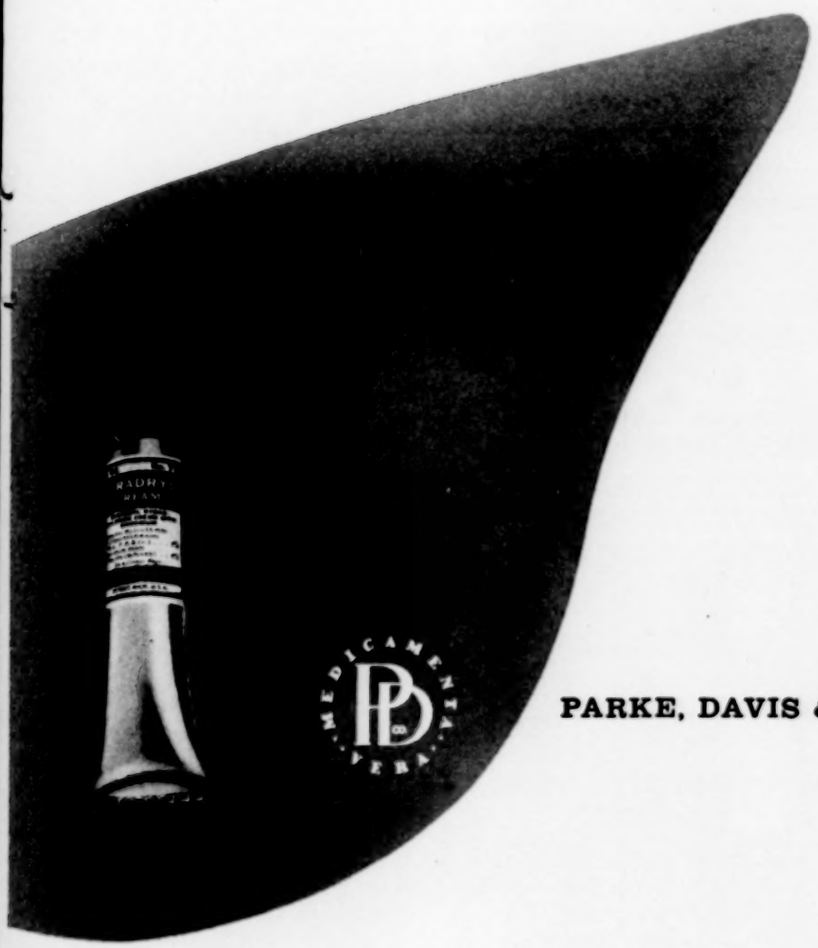

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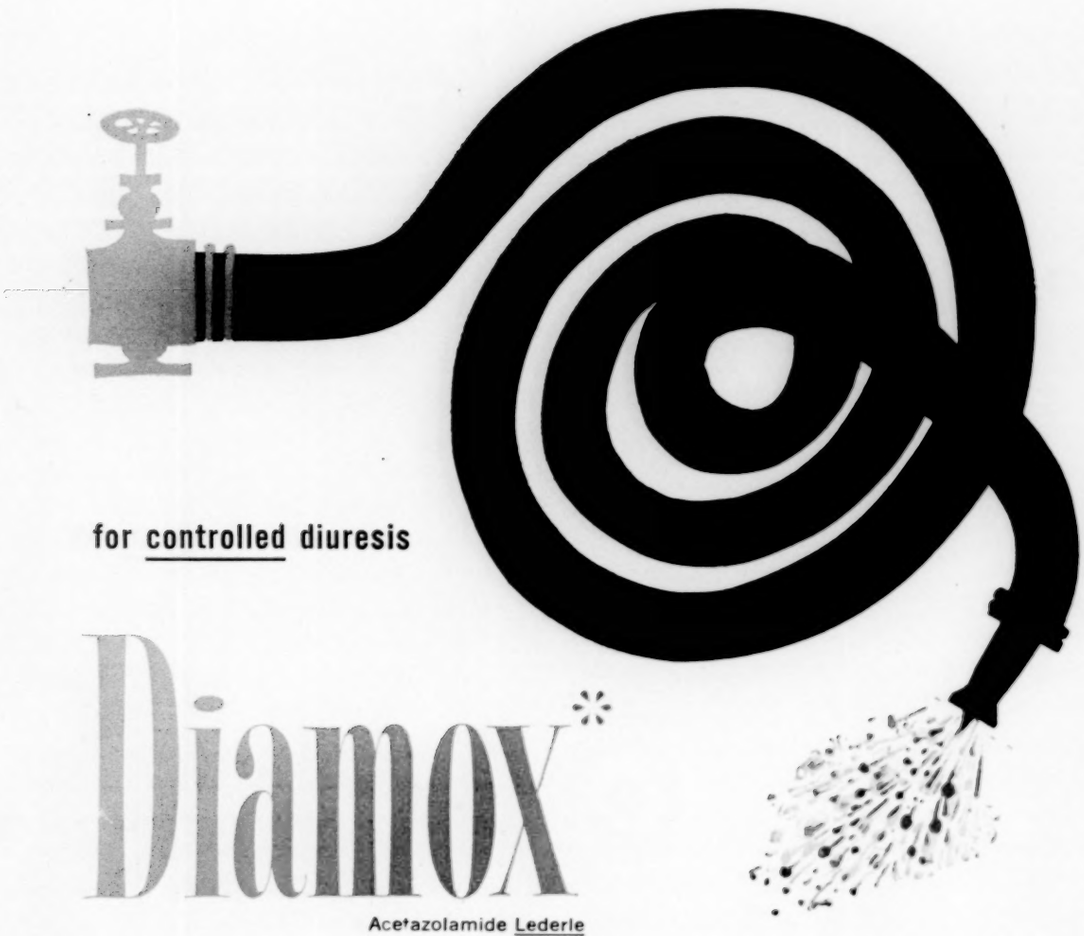

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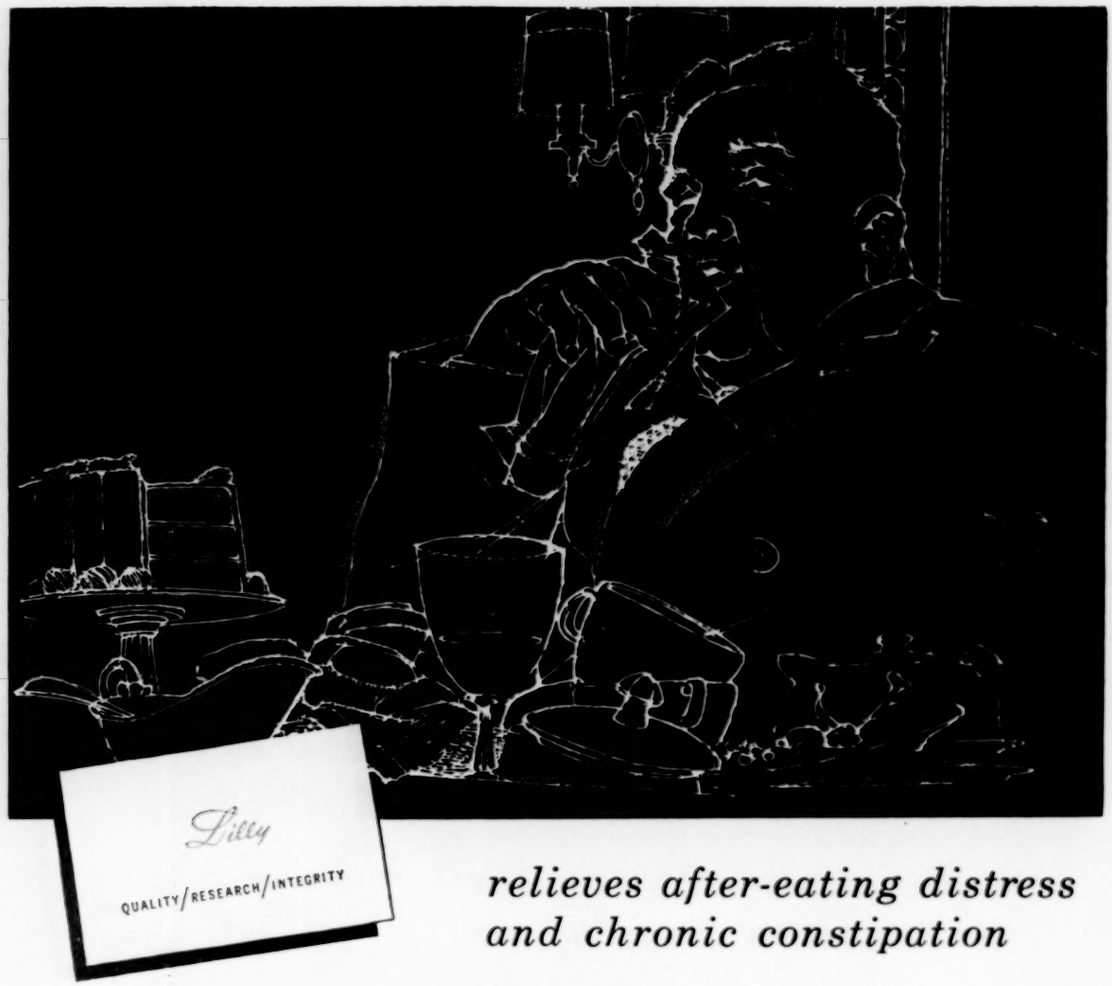

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The American Journal of Medicine

VOL. XXI AUGUST, 1956 NO. 2

Editorial

The Case for Viral Diarrheal Disease

AMONG the infectious diarrheal diseases there are several recognized etiologic agents. In the bacterial group the shigella, salmonella and some staphylococci are regarded as common and direct causes of diarrheal disease, although they may be present in stool specimens in the absence of diarrheal disease or any other apparent illness; the presence of one of these organisms in the stool of a patient suffering from diarrheal disease is usually taken as a proximate cause for the illness. Less well established as a direct bacterial cause of diarrheal disease are streptococci, the paracolon group and certain strains of Escherichia coli. Among intestinal protozoa, Endamoeba histolytica has long been considered causal in diarrheal disease, although it too may apparently live in the human intestine in various forms without producing diarrheal disease.[1] The role of other intestinal protozoa in the production of diarrheal disease is less well established. In the helminth group of intestinal parasites there is questionable correlation between the presence of diarrheal disease and a given helminth, at least in heavily parasitized persons.[1] Apart from these more or less certain causes of diarrheal diseases, the investigation of cases leaves a large residue in which no specific agent can be named as a certain or even likely cause for the illness.

The clinical diagnosis of the infectious diarrheal diseases is in some respects unsatisfactory. The clinician may make some etiologic surmise from the incubation period, mode of onset, diet history, exposure to toxic foods or chemicals, numbers of persons involved and course of the illness. Physical examination is usually unrewarding except to identify such unusual entities as paralytic poliomyelitis, typhoid or paratyphoid and to disclose non-infectious and non-intestinal causes for the symptom of diarrhea. On clinical grounds, the diarrheal disease complexes produced by bacteria, intestinal protozoa and helminths, poisonous foods or chemicals, systemic disease, or as a side effect of antibiotic therapy, present so many variants that no more than an informed guess is possible.

Appropriate laboratory procedures will establish with more or less certainty the presence or absence of specific protozoal, helminthic and bacterial pathogens, in particular those of the genus salmonella, shigella or staphylococcus in rectal swab or stool specimens. The presence in the stool of blood, mucus or macrophages may be of diagnostic value. In a fair number of instances bacteria or intestinal parasites of controversial significance in the causation of diarrheal disease are reported, and such findings must be weighed in the light of clinical judgment. With competent technical procedure and interpretation, establishment of the presence of protozoa and helminths should be accomplished in a large proportion of infested cases. The demonstration of shigella, however, is more difficult and probably no more than 70 to 80 per cent of isolations are made from stools which are positive for the organism when experienced technicians and scrupulous technic are in use. In the average hospital laboratory, with no special interest in stool bacteriology, and where "routine" stools are examined, the recovery rate for this delicate organism must be low.

[1] HIGGINS, A. R., FLOYD, T. M. and KADER, M. A. Studies in shigellosis. II. Observations on incidence and etiology of diarrheal disease in Egyptian village children. *Am. J. Trop. Med. & Hyg.*, 4: 271, 1955.

Even when the conscientious clinician has procured a fresh stool specimen or rectal swab and has had it delivered to the laboratory promptly, his efforts are not likely to be crowned with immediate success, if indeed he has success in culturing a bacterial pathogen. Some days are required in the laboratory for the demonstration of the "non-lactose fermenter"; and more days or weeks go by until the reference laboratory reports on the specific type of shigella or salmonella. This delay is understandingly discouraging to the clinician whose objective is to apply effective treatment and who is not helped in this respect. The advantages of the development of a new method of rapid identification of salmonella and shigella from clinical material are obvious. It might be added that this delay in bacterial stool diagnosis is a deterrent to many physicians in pursuing cultural methods of diagnosis, and gross under-reporting of cases of bacterial diarrheal disease probably results.

When all possible diagnostic procedures have been carried out in a case of infectious diarrheal disease, a large number of cases still remain in which no specific pathogen can be demonstrated. These cases of diarrheal disease, occurring sporadically, in small groups and in epidemics, have long been considered by clinicians to be due to an infectious viral agent, and many large and small epidemics of this type have been reported under a variety of names. No complete evidence has yet been adduced in proof of a viral agent in diarrheal disease, largely because such an agent has not been adapted to propagation in a laboratory animal or in tissue culture. It appears, however, that a reasonable body of evidence is at hand to postulate a viral agent as the direct cause of infectious diarrheal disease. Some of the important evidence for this etiologic relationship may be presented:

In 1943 Light and Hodes[2] produced diarrheal disease in calves by feeding a filtrate of stool from cases of epidemic diarrhea in newborn infants. Serial passage was made twenty-nine times in calves. The agent produced the disease in calves by parenteral inoculation of blood from sick calves and cross-infection occurred. The material was potent after freezing at −70°C. for two months.

[2] Light, J. S. and Hodes, H. L. Studies on epidemic diarrhea of the new-born; isolation of a filterable agent causing diarrhea in calves. *Am. J. Pub. Health*, 33: 1451, 1943.

In 1945 Reimann, Hodges and Price[3,4] reported on several epidemics of diarrheal disease in which a filtrate of stool, when nebulized and inhaled, produced similar illness in human volunteers. Oral feeding of the filtrate, however, was not effective in reproducing the disease.

Buddingh and Dodd,[5] working with stomatitis due to herpes simplex virus in 1944, reported finding a filtrable agent in mouth swabbings of infants and children suffering with stomatitis, fever and diarrhea, which produced a typical lesion differing from that produced by herpes simplex virus when inoculated on the cornea of a guinea pig. The agent could be serially passed in successive guinea pig corneas but could not be grown on chick embryo culture.

In a well documented report in 1947, Gordon, Ingraham and Korns[6] reported the production of diarrheal disease in human volunteers following oral administration of filtered stool suspension and throat washings from patients suffering from epidemic diarrhea in the Marcy State Hospital in Utica, New York. The disease could not be transmitted by inhalation of the filtered agent, and the agent could not be grown on embryonated eggs. The disease was carried through three passages in human volunteers. Some evidence of specific immunity was adduced by re-inoculation of volunteers and their failure to take the disease a second time within a short period. The average incubation period with this agent was three days, with usually rapid onset of nausea, vomiting and abdominal cramps, watery "pea-soup" stools and little or no fever. The illness was not severe and was self-limited.

Jordan, Gordon and Dorrance[7] in 1953 presented evidence for another non-bacterial

[3] Reimann, H. A., Hodges, J. H. and Price, A. H. Epidemic diarrhea, nausea and vomiting of unknown cause. *J. A. M. A.*, 127: 1, 1945.

[4] Reimann, H. A., Price, A. H. and Hodges, J. H. The cause of epidemic diarrhea, nausea and vomiting (viral dysentery?). *Proc. Soc. Exper. Biol. & Med.*, 59: 8, 1945.

[5] Buddingh, G. J. and Dodd, K. Stomatitis and diarrhea of infants caused by a hitherto unrecognized virus. *J. Pediat.*, 25: 105, 1944.

[6] Gordon, I., Ingraham, H. S. and Korns, R. F. Transmission of epidemic gastroenteritis to human volunteers by oral administration of fecal filtrates. *J. Exper. Med.*, 86: 409, 1947.

[7] Jordan, W. S., Jr., Gordon, I. and Dorrance, W. R. A study of illness in a group of Cleveland families. VII. Transmission of acute non-bacterial gastroenteritis to volunteers: evidence for two different etiological agents. *J. Exper. Med.*, 98: 461, 1953.

agent isolated from patients in a family study in Cleveland, Ohio. By means of human volunteers this agent ("FS") was compared with the "Marcy agent" isolated by Gordon et al.[6] The FS agent, fed as an unfiltered stool supernate, produced marked constitutional symptoms and was regularly associated with fever, in contrast to the Marcy agent, and showed an incubation period averaging twenty-seven hours. Evidence for specific immunity was demonstrated by appropriate experiments in volunteers. Disease was not produced in volunteers by inhalation of the FS agent. Inoculation of the material intracerebrally into rhesus monkeys or subcutaneously into suckling mice did not produce the disease.

Several relevant reports have appeared from Japanese workers. Yamamoto, Zennoyosi, Yanagita and Kato[8] in 1948 produced diarrheal disease in cats fed filtered suspension of stool from human cases, and made serial passages in cats. Stool filtrate also produced diarrheal disease in human volunteers when ingested, and one serial passage was made in human volunteers.

Kojima, Fukumi and Ishimaru[9] in 1953 reported that oral administration of stool filtrate from human cases, during an epidemic of some 10,000 cases of diarrheal disease, reproduced the disease in human volunteers. They regarded the disease as different from Gordon's "epidemic gastroenteritis," and observed an apparently high rate of clinical immunity in volunteers.

Gordon, Meneely, Currie and Chicoine[10] in 1953 reported transmission studies in human volunteers in the seventh serial passage of the filtered stool agent designated "Marcy" after three years storage on dry ice. Careful clinical observations, including blood, urine and cerebrospinal fluid examinations and liver function tests, revealed no significant abnormalities in the human volunteers who had been given the agent and in whom diarrheal disease had been produced. Attempted culture of the agent on human and guinea pig embryonic tissue failed to produce the disease when fed to volunteers.

Gordon[11] in 1955 presented an excellent orientation of clinical, epidemiologic and experimental evidence for the non-amebic, non-bacillary diarrheal disorders, and emphasized the necessity of better characterization of the agents by laboratory propagation and immunologic identification.

The ubiquity of diarrheal disease in clinical practice requires no emphasis to the clinician, and failure to identify a specific bacterial or parasitic cause is a usual happening. It is probable that sporadic cases, groups of cases or epidemics of diarrheal disease fall into the groups of infectious diarrheas propagated by filtrable agents. Even in areas of the world where bacterial diarrheas are endemic, and when the most scrupulous technics are used for the identification of pathogens, approximately 65 per cent of diarrheal episodes could not be assigned an etiologic agent.[1]

It appears then that there is impressive evidence that filtrable agents, or viruses, may be the proximate cause of several clinical syndromes which are frequently characterized by diarrhea. Among these syndromes may be included "epidemic non-bacterial gastroenteritis" of Gordon,[6] epidemic diarrhea of the newborn (Light and Hodes, 1943[2]), "stomatitis and diarrhea of infants" (Buddingh and Dodd, 1946[5]), "acute non-bacterial gastroenteritis" (Jordan et al., 1953[7]), "winter vomiting disease" (Goodall, 1954[12]), viral dysentery (Reimann, 1945[4]). There is apparently a wide spectrum of clinical disease produced by these agents, including more or less fever, nausea or vomiting, tormina, headache, malaise and, in most cases, diarrhea or, rarely, dysentery. As a group these infections appear to be mild and self-limited.

The infection has been reproduced in human volunteers by inhalation of the filtered agent (Reimann, 1945[3]); or by oral inoculation (Yamamoto et al., 1948[8]), (Kojima et al., 1953[9]), (Gordon et al., 1953[10]). The agent has been serially passed in human volunteers (Gordon et al., 1947,[6] 1953[10]), (Yamamoto et al., 1948[8]), (Kojima et al., 1953[9]); in cats (Yamamoto et al., 1948[8]); and in calves (Light and Hodes,

[8] Yamamoto, A., Zennoyosi, H., Yanagita, K. and Kato, S. Research in the causative agent of epidemic gastroenteritis which prevailed in Japan in 1948. *Japan M. J.*, 1: 379, 1948.

[9] Kojima, S., Fukumi, H. and Ishimaru, T. Epidemiology of "infectious diarrhea." *Japan. J. Med. Sc. & Biol.*, 6: 69, 1953.

[10] Gordon, I., Meneely, J. E., Jr., Currie, G. D. and Chicoine, A. Clinical laboratory studies in experimentally induced epidemic of non-bacterial gastroenteritis. *J. Lab. & Clin. Med.*, 41: 133, 1953.

[11] Gordon, I. The non-amebic, non-bacillary diarrheal disorders. *Am. J. Trop. Med. & Hyg.*, 4: 739, 1955.

[12] Goodall, J. F. The winter vomiting disease. A report from general practice. *Brit. M. J.*, 1: 197, 1954.

1943[2]). Evidence of specific strain immunity has been demonstrated in the human (Gordon et al., 1947[6]), (Jordan et al., 1953[7]), (Kojima et al., 1953[9]). No successful growth of the agent has yet been possible in laboratory animals or in tissue media.

Until these filtrable agents are grown and further studied by tissue culture, animal, human volunteer or other methods of study, it is pedantically inaccurate to state that viruses are the direct cause of these diarrheal syndromes. However, the available evidence would indicate that filtrable agents, presumably viruses, are in fact the cause of several types of infectious diarrheal disease, and that the clinician is justified, after proper negative search for bacterial and parasitic pathogens, in referring to these syndromes in such clinical terms as "virus gastroenteritis," "virus enteritis," "virus diarrhea" or "virus dysentery." It well may be that these virus infections of the human intestine constitute a major portion of infectious diarrheal syndromes.

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Clinical Studies

Clinical and Laboratory Studies in Patients with Respiratory Disease Caused by Adenoviruses* (RI-APC-ARD Agents)†

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Acute febrile respiratory illnesses are a major cause of disability in civilian and military populations. Viruses belonging to the recently discovered RI family,[1–6] which is also called the APC family[7–10] and includes agents designated ARD,[11–13] have been shown to be the cause[2–4,6,11,12] of most cases of acute respiratory illness in military recruit populations; these clinical diseases in the recruits are undifferentiated acute respiratory disease (ARD), non-streptococcal exudative pharyngitis and primary atypical pneumonia unassociated with cold or streptococcus MG agglutinins. These maladies were recognized during the early 1940's by the Commission on Acute Respiratory Diseases[14–18] on epidemiologic and clinical grounds and on the results of transmission experiments in human volunteers. Viruses of this same family have also been found to cause epidemics or sporadic cases of pharyngoconjunctival fever and acute respiratory illnesses[7–10,12] in civilian persons, primarily in children. The agents of the family are heterogeneous antigenically[1,5,6,8,9] and comprise a group of distinct serotypes.[8,9]

The discovery of the etiologic agents which cause most of these illnesses, together with the development[1,5,6,8,9] of laboratory methods for definitive diagnosis, has made possible the description of the clinical picture in proved cases of RI infection. The present paper describes the clinical and laboratory findings in forty-five patients who were sick with RI virus infection at Fort Dix, New Jersey, during January, 1954.

CLINICAL MATERIALS AND METHODS

The patients studied were United States Army recruits in basic training at Fort Dix, New Jersey, who were admitted to the hospital with a febrile acute respiratory illness on January 10, 11 or 12, 1954, during an epidemic. Fifty patients were chosen at random from among soldiers hospitalized following preliminary observation at their unit dispensaries. Each patient had a temperature of 100°F. or greater on admission, and the duration of the acute illness prior to hospital admission did not exceed four days. Of the fifty persons examined, forty-five were shown by laboratory tests to be suffering from infection with RI virus; the findings recorded here are limited to the latter group. All of the soldiers studied were between eighteen and twenty-three years of age and had been inducted into the army during the previous three weeks.

Detailed clinical observations were made on each patient before entrance into the hospital and for five consecutive days after admission. Later examinations were made by the medical officers assigned to the wards. The initial clinical study consisted of careful interrogation of the patient for a description of past and current illnesses and a complete hospital admission type of physical examination. Particular care was given to critical inspection of the head, neck and respiratory system.

Symptomatic treatment consisting of bedrest with adequate fluid intake, aspirin and codeine, expectorants and steam inhalation for relief of cough was employed in all patients. In addition, during the period of this particular study all hospitalized patients with respiratory disease were given 2 gm. of terramycin® per day for seven days as part of the standard treatment for this illness.

* These viruses, formerly known as RI, APC or ARD agents, have recently been designated the Adenoviruses.

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The specimens for laboratory study were taken immediately after physical examination and just prior to admission to the ward. A throat culture was made on a blood agar plate for routine bacteriologic examination. For the virus isolation work throat washings were collected in 15 ml. of veal infusion broth, divided into aliquots, and stored frozen in sealed glass ampoules in the dry ice refrigerator until tested. Blood samples for serologic study were collected at this time and again two and four weeks later. Roentgenograms of the chest and total and differential white blood cell counts were made prior to admission to the hospital and again as indicated by the clinical course. In most instances the x-rays were repeated within seven days following hospitalization.

LABORATORY MATERIAL AND METHODS

RI Group Infection. Serum neutralization and complement-fixation (C-F) tests with RI viruses and patients' serums were performed according to methods already described.[1] C-F tests were done on all serums, and neutralization tests on a portion. The latter tests were carried out in HeLa cell tissue cultures[19] using type 4 strain (RI-67),[1] type 7 virus (strain RI-4-202 recovered in the present study) recently named by Berge et al.[20] and, in certain instances, the particular strain of virus which had been recovered from the patient. The C-F antigen employed in the tests was prepared from HeLa cell cultures infected with the RI-67 strain. The active antigen in such material is a "soluble substance" which is elaborated by the viruses of the RI family[2,5,6,9,21] and may be employed to detect infection with all of the known types. The isolations of RI viruses from throat washings were accomplished in HeLa cultures employing the same general methods described earlier.[1] By this procedure 0.1 ml. amounts of the throat washings from the patients stored frozen at −70°c. after collection for periods of two months to one year were inoculated into the HeLa culture tubes. If no cytopathogenic effect was observed within three days' incubation at 36°c., the tissue and fluid were treated in a Mickle tissue disintegrator, centrifuged lightly to remove débris and passed to new tubes. Cultures failing to show typical degeneration in two passages were discarded. The recovered viruses were typed by the serum neutralization technic,[1] using monotypic rabbit antiserums according to the system of Rowe et al.[9]

To rule out other infections the diagnostic hemagglutination-inhibition (H-I) tests for influenza were performed by the method recommended by the Committee on Standard Serological Procedures in Influenza Studies,[22] using the acute phase and the two- and four-week convalescent serum specimens and human "O" erythrocytes. The cold and streptococcus MG agglutination tests, which become positive in certain kinds of atypical pneumonia but not in RI infections, were carried out by standard procedures already described.[23,24] Antistreptolysin tests for streptococcal infection were performed with all three serum samples from all patients by the method of Rantz and Randall.[25]

EPIDEMIOLOGY

At the time the present patients were selected for study (January 10–12, 1954) an epidemic of respiratory disease was in the rising phase with the "total respiratory disease" rate per 1,000 per year being 540 for the week ending January 13th.[4] At this time there were no notable epidemics at Fort Dix of known etiology other than the RI group infections. Influenza was largely absent throughout the world during 1954[26] except for a sporadic occurrence of influenza B. This was also true of Fort Dix.

LABORATORY FINDINGS IN PATIENTS WITH RI INFECTION

All forty-five patients in the current study showed a diagnostic (fourfold or greater) rise in C-F antibody level against RI virus. Three gave a fourfold increase, twelve an eightfold rise, and the elevations in titer in the remaining thirty-two cases were between sixteenfold and sixty-four fold. Of the twelve patients whose serums were examined by the neutralization method, all showed a significant rise in antibody titer against type 7 virus and eight also displayed a rise against type 4 virus. The neutralization findings in eleven of these cases have been recorded elsewhere (ref. 6, Table v, type 7 cases). Attempts at isolation of virus employing throat washings from each of the forty-five patients yielded RI virus in eleven instances. Each of the isolates was identified as type 7. These findings established the diagnosis of RI infection in the forty-five patients selected for study and showed that the type 7 agent was predominantly or exclusively present.

Tests for antibodies against influenza A, B and C viruses were performed on serums from all forty-five patients; in no instance was there evidence of recent infection with these agents. Similarly, none of the patients showed a significant increase in cold or streptococcus MG agglutinin. The cultures of the throats of the patients failed to reveal a primary bacterial etiology among the cases studied. Only one patient showed a significant increase (rise from 50 to 100 units) in amount of antistreptolysin. Beta hemolytic streptococci were present in the throats of a few individuals, but the fact that significant increases in antistreptolysin failed to

develop in these particular patients excluded streptococci as the primary etiology.

CLINICAL OBSERVATIONS

It was obvious quite early in the study that infections of man with RI viruses are not manifest as a single classic syndrome. Rather, the symptoms and clinical signs, while referable primarily to the respiratory tract, are quite protean and diverse. Furthermore, this diversity does not appear to be related simply to the severity of clinical symptoms. For clarity, therefore, the composite clinical picture as determined from the forty-five patients with proved RI infections severe enough to require hospitalization is presented before the case records of five representative patients are reviewed.

TABLE 1
MISCELLANEOUS OBSERVATIONS AMONG FORTY-FIVE PATIENTS WITH RI GROUP VIRUS INFECTIONS

Observations	Mean	Standard Deviation	Range
Maximum temperature	102.9°F	1.0°F.	100.3°–104.2°F.
Duration of fever (days)	5.5	2.2	2–12
Duration of hospitalization (days)	9.7	6.8	4–36
Admission white blood cell count $\times 10^3$	12.2	4.0	7.1–33.0

The Composite Clinical Picture. The occurrence of the more common symptoms and signs in the study group of forty-five patients is presented in Figure 1. In this chart the ruled bars summarize the occurrence of individual symptoms or signs on initial observation and the solid bars show the occurrence of symptoms or signs both initially and during the hospital course.

Onset. All of the patients were recruits who had been inducted into the Army during the three-week period before their hospitalization. During this time in each recruit minor but obvious respiratory symptoms (nasal obstruction, mucoid or mucopurulent nasal discharge, or productive cough) had developed and all complained of easy fatiguability. The onset of the acute illness requiring hospitalization was superimposed upon the existent minor respiratory complaints. In about two-thirds of the cases the onset was gradual; feverishness, pharyngitis, cough with hoarseness, malaise, myalgia, headache, asthenia and dizziness increased in severity over a period of two to four days before medical care was sought. By contrast, the remaining one-third of the patients had a sudden onset of chills and fever accompanied by the aforementioned symptoms during a period of twenty-four hours prior to admission.

Clinical Features. The most common clinical features presented by patients upon hospital admission were fever, pharyngitis and usually non-productive cough. The soldiers were all acutely ill, appearing listless and haggard. The maximum temperature during hospitalization ranged from 100.3 to 104.2°F. (mean 102.9°F.) and lasted two to twelve days (mean 5.5 days). The period of confinement ranged from four to thirty-six days and averaged about ten days. (Table 1.)

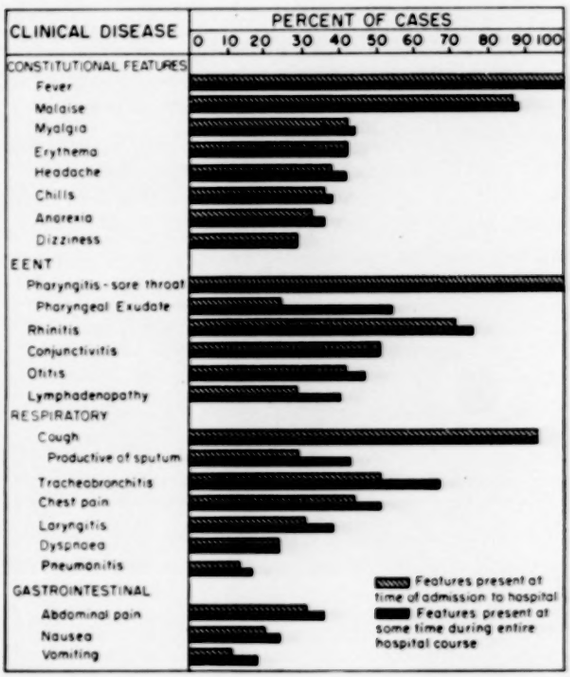

FIG. 1. Summary of clinical features in forty-five hospitalized cases of respiratory illness caused by RI virus.

Vital Signs. In most patients the fever was maximal at the time of admission with subsequent defervescence by lysis. The pulse rate usually was elevated to a degree commensurate with the height of the fever, although nine patients manifested relative bradycardia with dicrotism. The respiratory rate was variable, increasing after paroxysms of cough but otherwise remaining normal.

Constitutional Features. Thirty-nine of the patients (87 per cent) complained of malaise at the time of admission but the remaining six might have been able to continue their duties had the

respiratory symptoms been less debilitant. The myalgia of the extremities and back which occurred in about 40 per cent of the cases was slight, while that of the abdominal and chest muscles was more prominent and was usually attributable to the severe, persisting cough. Ocular myalgia occurred in only three patients. A marked persisting erythema of the skin of the head, neck and thorax was observed in nineteen patients (42 per cent) whose admission temperatures were 102°F. or greater. The flushed skin was warm, blanched on pressure and was not modified by paroxysmal coughing. Seventeen of the patients (38 per cent) experienced frank chills. Anorexia was mild and occurred in 36 per cent of the cases. Dizziness with asthenia was present in 29 per cent of the patients and was intensified by coughing. The headache, when present, was moderately severe and was described as "sinus" in origin, involving the frontal and retro-ocular regions. It was increased by severe coughing or by leaning forward.

Eye, Ear, Nose and Throat Manifestations. The throat discomfort was described in half of the patients as severe pain in the anterior cervical region radiating to the ears. Roughly half of the group complained of a burning sensation of the posterior pharynx or pain and tenderness of the soft palate, thyroid cartilage and muscles of deglutition, resulting, in a few patients, in dysphagia and dysarthria of varying degree. The appearance of the throat was abnormal in all patients. During the initial phase of the disease the mucous membranes were intensely red and edematous, and the uvula was occasionally two to four times its normal size. Bright red petechiae were seen infrequently at the base of the uvula. By the second day of acute illness intensely erythematous hyperplastic patches or vertical bands of lymphatic tissue appeared on the posterior and lateral walls of the pharynx and extended to the pyriform sinuses. The inflamed mucosa of the pharynx was less erythematous and usually appeared pale in contrast to the intense red color of the lymphatic tissue. The lingual tonsils were enlarged and the faucial tonsils, when present, were hypertrophied and cryptic. During the first few days the hyperplastic lymphatic tissues usually showed little if any exudate, but by the third day of disease small patches of white exudate (0.2 mm. to 0.5 mm. in diameter) appeared on the pharyngeal and tonsillar lymphatic tissue and occasionally on the uvula. By the fourth day of disease 54 per cent of the patients exhibited exudate. The patches of exudate became enlarged and in certain instances confluent. These were attached firmly to the underlying tissue and showed no erythematous areola. Most of the exudate, as well as other pharyngeal signs and symptoms, had disappeared by the seventh day of illness. In addition to exudate, purulent postnasal discharge was found occasionally in the throat.

Lymph node involvement, evident in 40 per cent of the cases, consisted of enlargement (1 to 2 cm. in diameter) in the anterior and posterior cervical, posterior auricular and supraclavicular regions. These nodes were freely movable and were neither matted nor fluctuant. Cervical nodes, palpable at the time of the initial physical examination, subsequently increased in size and number as the pharyngitis reached its maximum. Thus the glands were most prominent when exudate was present on the hyperplastic lymphatic tissue of the pharynx and regressed slowly as the mucosa returned to the natural condition. However, lymphadenopathy always persisted several days after the pharynges appeared normal. None of the glands except the "tonsillar nodes" located inferiorly to the angle of the mandible was sensitive to palpation. Axillary, epitrochlear or inguinal nodes were palpable in ten of the patients on admission. These resembled the cervical and supraclavicular glands but remained unchanged during the period of observation; thus they did not appear to be connected with the respiratory disease.

Conjunctivitis, which lasted one to three days after admission, occurred in twenty-three of the patients (51 per cent). This was bilateral and mild, consisting of erythema and granularity of the conjunctivas and scleras, particularly at the limbus and in the region of the nasal canthi where edema was also present. A scanty serous exudate which caused crusting of the eyelids during sleep was commonly present. Burning sensation behind the eyelids and photophobia were the chief complaints. However, three patients manifested chemosis of the eyelid in addition to conjunctival congestion, and in one of these patients there was purulent yellow exudate from the swollen eyes.

Thirty-five of the patients (76 per cent) exhibited rhinitis characterized by serous, mucopurulent or occasional purulent discharge from the erythematous and edematous nasal mucosa.

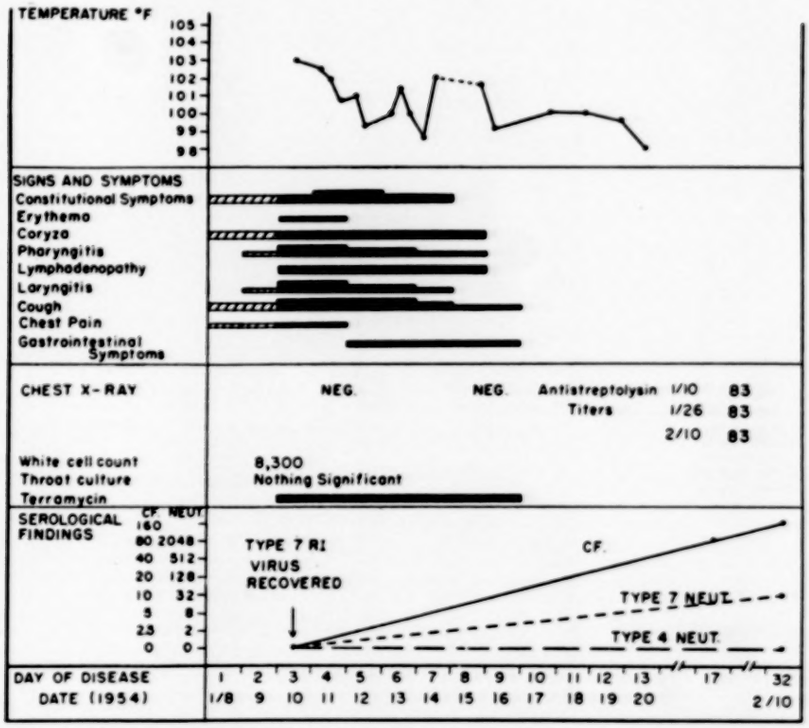

FIG. 2. Case 4-202. Clinical course and laboratory findings in a typical case of undifferentiated acute respiratory disease (ARD).

These patients complained of obstructed nares or nasal congestion intensified by exposure to cold air. A history of sneezing, copious watery discharge or tender nostrils was not elicited in any case. Catarrhal otitis media and externa were present in about half of the patients, consisting of congestion and diffuse erythema of the mucosa of the external auditory canal, the margins of the tympanums and of Shrapnell's membranes.

Respiratory Manifestations. Laryngitis characterized by hoarseness and persistent irritation was present in 38 per cent of the patients. In a few patients who were examined by indirect laryngoscopy the vocal cords and tracheal mucosa were found to be intensely red and edematous. Forty-two of the forty-five patients (93 per cent) had a debilitating cough which occurred simultaneously with the pharyngitis and which progressed rapidly from a dry hack at the time of onset to unrelenting paroxysms. Such episodes aggravated existing symptoms and provoked pain in the intercostal and costal muscles of the chest (51 per cent), dyspnea, vomiting and syncope. In one instance the cough was severe enough to cause rib fracture. The cough was productive of sputum in thirteen of the patients (29 per cent) at the time of admission and in six additional persons during the hospital course. The sputum was usually purulent and was streaked with blood in a few instances. In five patients with pneumonitis increased volume and discoloration of the sputum coincided with signs of resolution.

Lower respiratory tract involvement consisting of tracheobronchitis including bronchiolitis (67 per cent) and pneumonitis (16 per cent) was prominent among the patients. Tracheobronchitis was indicated by coarse rales and rhonchi. Additional signs such as inspiratory lag, diminished breath sounds, and sibilant and post-tussic inspiratory rales were considered indicative of bronchiolitis and pneumonitis. The latter entities were clinically indistinguishable in the absence of signs of consolidation. The differential diagnosis was based on the chest x-ray findings. The dyspnea (24 per cent) which was present in all patients with pneumonitis and in four additional persons with severe cough was relatively mild and oxygen therapy was unnecessary.

Gastrointestinal Manifestations. Abdominal pain involving the epigastrium and paraumbilical regions occurred in 34 per cent of the

patients. This was associated with muscle tenderness only and was most marked in patients who experienced intractable cough. Nausea was present in nine patients (20 per cent) and vomiting in five (11 per cent) at the time of admission. These symptoms were usually an

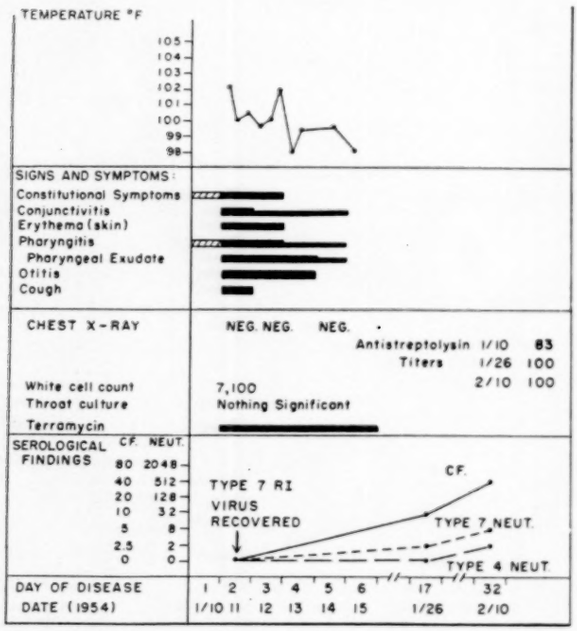

FIG. 3. Case 4-215. Case illustrating non-streptococcal exudative pharyngitis with conjunctivitis.

immediate sequel to severe cough. Nausea, vomiting and diarrhea developed in a few additional patients after hospitalization, at a time when terramycin therapy was being given, suggesting iatrogenic rather than infectious etiology.

White Blood Cell Count. The white blood cell count (Table 1) ranged from 7,100 to 33,000/cu. mm. with a mean of 12,200 cells. The elevated count, when present, was associated with an increase in neutrophils.

CASE REPORTS

Case 4-202. (Clinical diagnosis: undifferentiated acute respiratory disease (ARD).) With the onset of cold weather on January 6, 1954, complete nasal obstruction developed in this twenty year old white soldier. (Fig. 2.) Two days later on January 8th, after field training, the patient noticed diaphoresis, non-productive cough, continuous non-pleuritic pain in the right thorax and a slightly stiff neck without headache. The next day he resumed field training but was anoretic, hoarse and near exhaustion. By the morning of January 10th the severity of these symptoms had increased and the patient had a sore throat, chills and drowsiness, with hamstring and abdominal myalgia. He reported to the outpatient clinic in the early evening complaining of feverishness, vomiting and sore throat. On admission the temperature was 103°F., pulse 98 and respirations 18. There was marked erythema of the face and upper trunk which blanched on pressure but no rash was present and the conjunctivas and scleras were clear. The nasal mucosa was edematous and mucoid discharge was present. The pharyngeal mucous membrane was intensely injected, edematous and granular, and the mucosal edema extended to involve the hypopharynx and vocal cords. No exudate was present in the throat; the anterior cervical lymph nodes were palpable but not tender. The lungs were clear to percussion and auscultation and the remainder of the physical examination revealed no abnormalities.

The total white blood cell count was 8,300/cu. mm. (polymorphonuclears, 84; lymphocytes, 16). The throat culture was essentially negative for bacterial pathogens and the antistreptolysin titers were unchanged. Chest x-rays revealed no abnormalities.

The fever lasted for six days following admission and was associated with persisting coryza, pharyngitis, laryngitis and general malaise. During this period the cough was severe, contributing to insomnia and general discomfort. Repeated chest x-rays revealed no abnormalities. Except for a mild diarrhea associated with terramycin therapy, convalescence was uneventful. The patient was asymptomatic when returned to duty on January 20th, thirteen days after the onset of illness.

Comment: The illness in this patient closely resembles the syndrome of undifferentiated acute respiratory disease (ARD) with non-bacterial pharyngitis and laryngitis. The associated gastrointestinal symptoms presumably were related to terramycin therapy. Laboratory diagnosis of RI group infection in this patient was provided by the recovery of virus (type 7) and by the demonstration of a significant increase in the amount of C-F and type 7 neutralizing antibody.

Case 4-215. (Clinical diagnosis: non-streptococcal exudative pharyngitis with conjunctivitis.) The patient, a twenty-two year old white man, had coryza and occasional cough for two weeks prior to onset of the acute illness. (Fig. 3.) On January 9th he felt unusually tired and on the following day a severe sore throat developed with dysphagia, chilliness and pain in the legs and lower back. At this time his temperature was 102.2°F., pulse 90 and respirations 15 per minute.

On admission on January 11th the patient was acutely ill and exhibited erythema of the face and upper trunk which blanched on pressure. Paroxysmal bouts of coughing, which were productive of mucopurulent sputum, occurred almost continuously. The conjunctivas of both eyes were granular and, together with the scleras, were injected, particularly at the limbus; the corneas were grossly clear. The

mucosa of the external auditory canals was erythematous but the tympanums were not inflamed. The pharyngeal mucosa was intensely injected and covered by mucopurulent postnasal discharge. The heart was normal although the rate was slow in relation to fever; the radial pulse was dicrotic. The lungs were clear to percussion but rhonchi were audible over the lower left lung field anteriorly and laterally. The abdomen was normal.

On January 11th the white blood cell count was 7,100/cu. mm. (neutrophils, 76; lymphocytes, 13; monocytes, 13). Hemophilus influenzae was present in throat cultures in such small numbers as to be considered insignificant. There was no significant increase in the antistreptolysin titer during the four weeks of observation. X-ray examination of the chest showed slightly increased bronchovascular markings at the right base of the lung.

After admission to the respiratory disease ward symptomatic and terramycin therapy were administered. The patient's fever persisted until the fourth day of illness. The initial edema of the pharyngeal mucosa subsided and large red patches of lymphoid tissue appeared. Pinhead-sized areas of white exudate surmounted the lymph follicles in the throat. These remained discrete and resolved gradually as throat pain diminished. The chest findings were normal.

Comment: The disease in this patient was primarily exudative pharyngitis of non-bacterial etiology. The conjunctivitis, which was bilateral, was of a mild follicular type without purulent exudate and was typical of that commonly experienced by patients in the epidemic. The etiology of the disease was established by the recovery of type 7 RI virus and by the demonstration of a significant increase in C-F and neutralizing antibody.

Case 4-239. (Clinical diagnosis: non-streptococcal exudative pharyngitis with tracheobronchitis and bronchiolitis.) The patient, a twenty-one year old white man, noted fever during the morning of January 10th associated with cough, drowsiness, dizziness, anorexia and vomiting. (Fig. 4.) On the following day malaise, fever, sore throat and cough were present and the patient was admitted to the hospital. The temperature was 100.2°F. and pulse and respirations were 110 and 18, respectively. The patient manifested an acute illness of moderate severity characterized by paroxysms of non-productive cough with associated dizziness and vomiting. The pharyngeal mucous membrane was injected and showed extensive lymphoid hyperplasia. Numerous patches of white exudate measuring about 0.2 mm. in diameter surmounted the bands of hyperplastic lymphatic tissue present in the posterior pharyngeal wall. The eyes and nose were clear but the external auditory canal and tympanum of the right ear were diffusely erythematous and injected. There was equal expansion of both sides of the thorax, but crepitant and sibilant rales were audible at both bases anteriorly and over the right lower lung area posteriorly. No other abnormalities were present.

The white blood cell count was 13,800/cu. mm. (neutrophils, 81; lymphocytes, 17; monocytes, 2). The throat culture revealed the presence of Neisseria catarrhalis, alpha hemolytic streptococci and a small

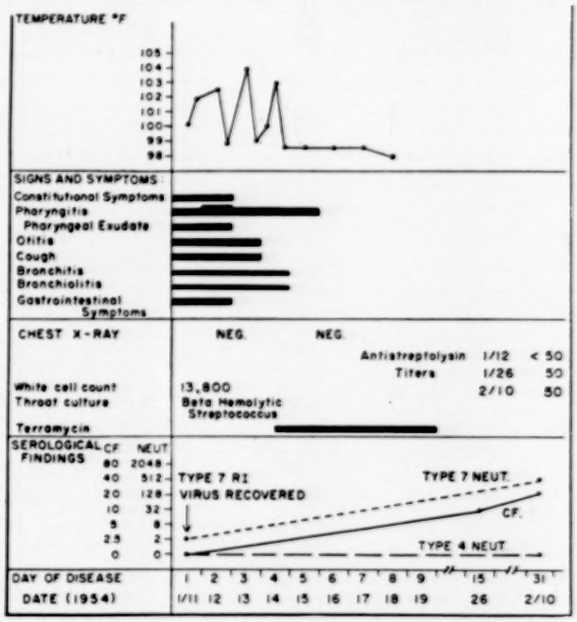

FIG. 4. Case 4-239. Findings in case of non-streptococcal exudative pharyngitis with tracheobronchitis and bronchiolitis.

number of beta hemolytic streptococci. The tests for antistreptolysin were non-diagnostic for streptococcal disease.

Following admission to the hospital the patient's symptoms increased in severity, the temperature reaching 104°F. on January 13th (the fourth day of illness). At this time there was increased edema and erythema of the pharynx but the exudate in the throat was less apparent. Post-tussive rales were audible over both lung fields anteriorly and posteriorly in areas corresponding with the lower lobes. On January 14th terramycin therapy was begun coincident with beginning defervescence. The following day the patient was afebrile; his throat was less erythematous and no follicles or exudate was present. The lungs were clear on physical examination. The ensuing course was uneventful and no subsequent complications were noted.

Comment: This patient had ARD initially which culminated in non-streptococcal exudative pharyngitis and accompanying signs of tracheobronchitis and bronchiolitis. The laboratory diagnosis of RI infection was made by recovery of type 7 virus from the throat washings and by the demonstration of significant increase in C-F and neutralizing antibody against the agent during convalescence. Presumably,

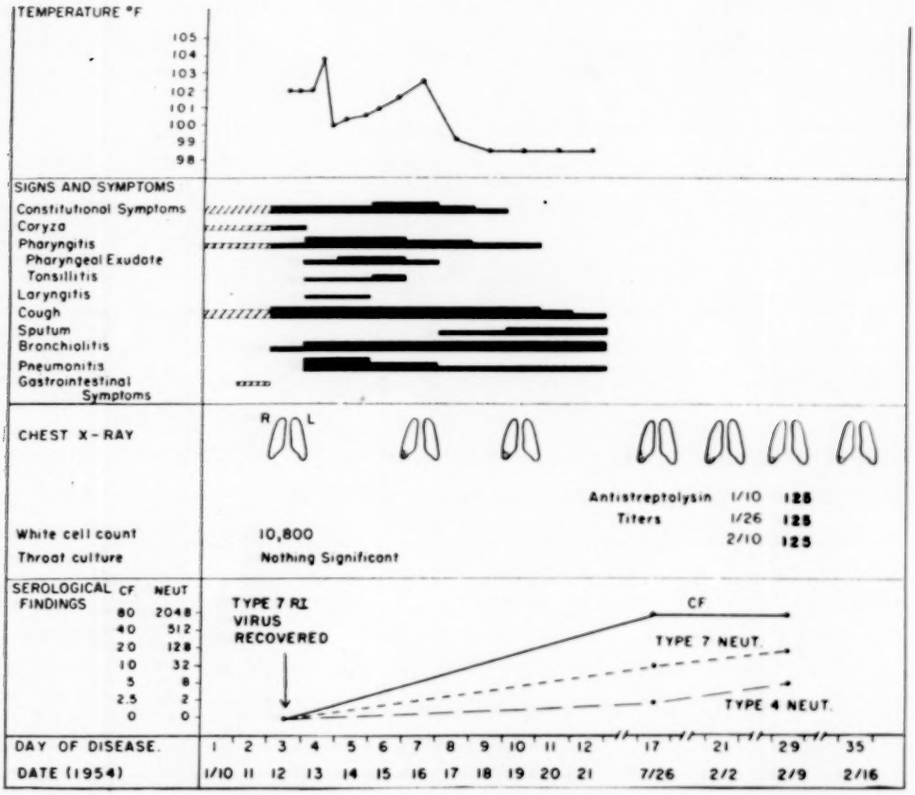

FIG. 5. Case 4-229. Patient with bronchial pneumonitis with atelectasis and non-streptococcal exudative pharyngitis.

the defervescence was not related to antibiotic therapy.

Case 4-229. (Clinical diagnosis: pneumonitis with atelectasis and non-streptococcal exudative pharyngitis.) This patient, an eighteen year old white man, complained of nasal discharge and cough for two weeks prior to onset of the acute illness on January 10th. (Fig. 5.) At this time the cough became more severe and productive and was associated with abdominal tenderness. Generalized malaise, severe headache which was intensified by leaning forward, and burning pain in the lumbar region contributed to the patient's discomfort.

At the time of hospital admission the patient's temperature was 102°F. and the pulse and respiratory rates were 100 and 16 per minute, respectively. He appeared acutely ill and suffered repeated paroxysms of coughing. There was crusting and purulent exudate in the exterior nares and redness in the external auditory canal of the right ear. The throat was slightly erythematous and without exudate, but a few bright petechiae were present on the base of the uvula. Dullness to percussion was heard over the right lower chest where crepitant rales were audible during inspiration. Palpation of the abdominal wall elicited tenderness of the muscles.

On January 12th the white blood cell count was 10,800/cu. mm. (neutrophils, 90; lymphocytes, 9; monocytes, 1). Culture of the throat revealed a normal flora of alpha hemolytic streptococci, H. influenzae and Staphylococcus albus. There was no increase in antistreptolysin titer in the progress of the illness. The x-ray of the chest was negative at this time. (Fig. 6.)

The patient's illness became more severe during the first five days in the hospital. He complained of sore throat and more intense cough, despite cough mixtures and analgesics. On January 13th the pharyngeal mucosa and the uvula were edematous and pinhead-sized areas of firmly adherent white exudate were present on the hyperplastic lymphatic tissue of the posterior surface and anterior pillars of the pharynx. During the three days following, the mucosa between the hyperplastic areas became pale and less edematous and the amount of exudate was increased, becoming confluent on the anterior pillars. On January 12th there was an obvious inspiratory lag on the right side of the chest together with dullness to percussion posteriorly over the lower chest. Bronchial breath sounds were heard over the posterior and postero-lateral lung base and the crepitant rales were audible during inspiration following voluntary cough. These findings persisted through January 15th and on January 16th a chest x-ray revealed increase in the peribronchial densities radiating inferiorly to the diaphragm. (Fig. 7.) Nodular but soft radio-opacities

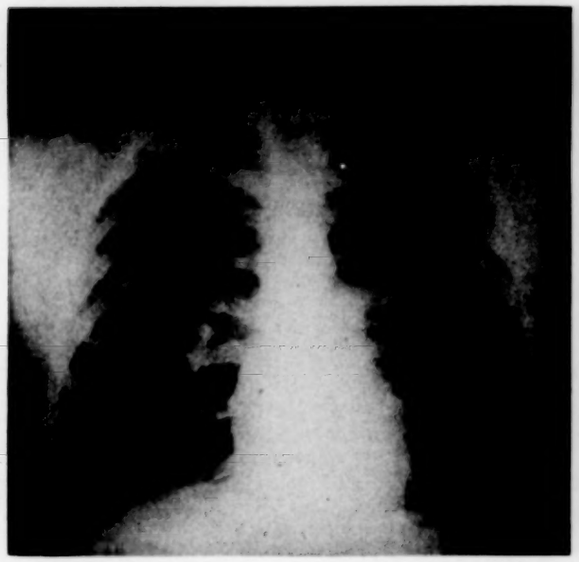

FIG. 6. Appearance of lungs of Case 4-229 (Fig. 5) on January 12th prior to development of positive x-ray findings.

FIG. 7. Case 4-229. The findings on January 16th. Note the nodular densities laterally at the level of ribs nine and ten posteriorly, together with shadows presenting a "ground glass" appearance and partially obstructing the costophrenic angle.

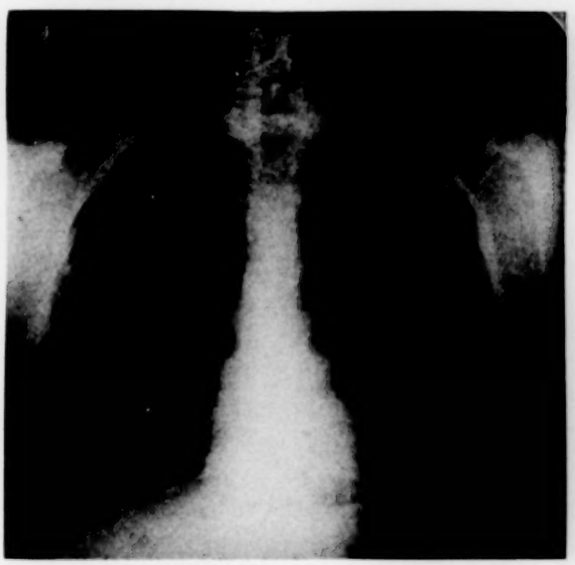

FIG. 8. Case 4-229. X-ray taken February 2nd shows that the bronchovascular markings were still slightly greater than normal but the nodular opacities had resolved. The right costophrenic angle was obliterated by a shadow suggestive of atelectasis.

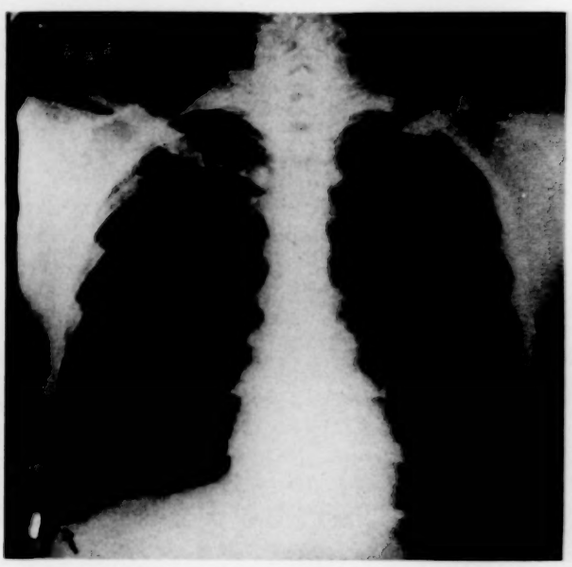

FIG. 9. Case 4-229. This x-ray taken February 9th shows the resolution of the peribronchial infiltration with a residual linear density remaining at the costophrenic angle.

gave a lightly mottled appearance to the lung laterally at the ninth to tenth posterior ribs. The costophrenic angle was visible but partially obscured by a ground glass haze suggesting pleural reaction or atelectasis. Subsequent chest x-rays revealed similar but decreasing shadows. Right lateral views of the chest on January 19th revealed a homogeneous density of triangular shape with its apex at the lower hilar region, its base obscuring the posterior sulcus. This was interpreted as due to atelectasis or infiltration. On February 2nd the bronchovascular markings were still slightly greater than normal but the nodular opacities had resolved. (Fig. 8.) The right costophrenic angle was obliterated by a band-like shadow which was reduced to a linear density by February 9th, suggesting a residuum of localized atelectasis.

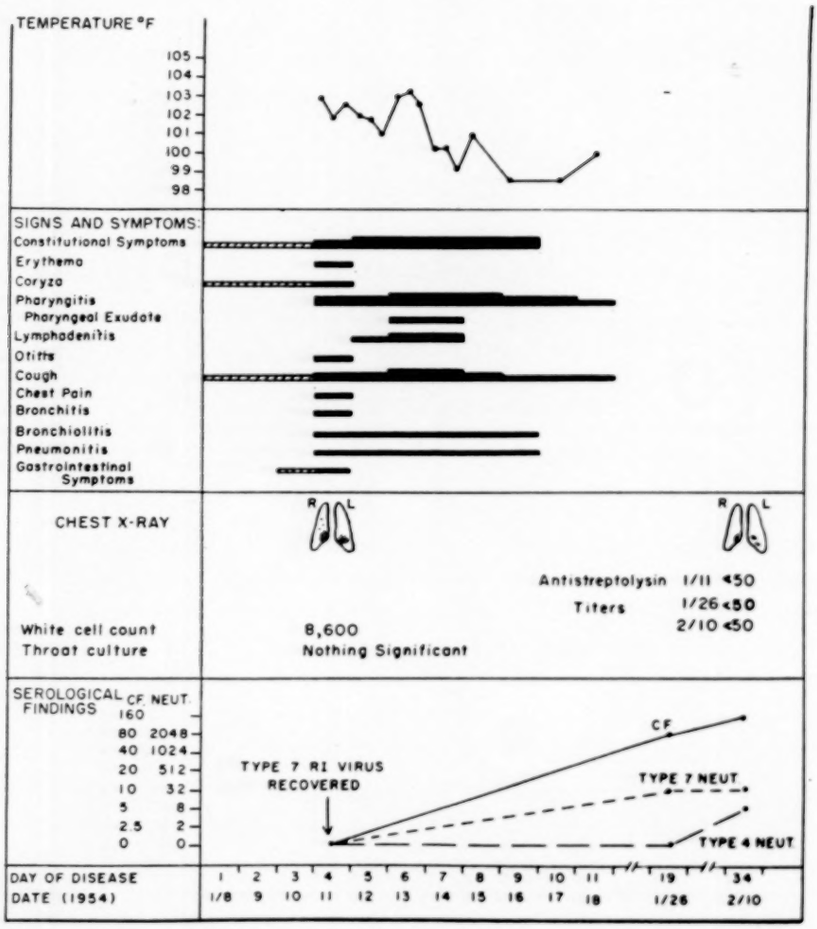

FIG. 10. Case 4-207. This patient had primary atypical pneumonia with tracheobronchitis and non-streptococcal exudative pharyngitis.

(Fig. 9.) The patient improved rapidly after the seventh day of illness but was hospitalized until Februay 16th at which time the pneumonitis and atelectasis had almost completely cleared.

Comment: This patient's illness represents respiratory infection which progressed from ARD to exudative pharyngitis and finally bronchitis, bronchiolitis and pneumonitis with localized atelectasis. Laboratory diagnosis of type 7 RI infection was established by the recovery of virus from throat washings and the increase in C-F and neutralizing antibody in the progress of the disease.

Case 4-207. (Clinical diagnosis: primary atypical pneumonia with non-streptococcal exudative pharyngitis and tracheobronchitis.) In this twenty-three year old white man, symptoms of mild coryza, occasional chilliness without fever and flushed face developed about January 5, 1954. (Fig. 10.) On January 8th the patient had a non-productive cough sufficiently severe to interrupt sleep, and on the following day he was aware of malaise, burning eyes and chilliness together with persistent cough. By January 10th the cough was sufficiently severe to cause vomiting and there was feverishness, sweating and insomnia provoked by low back pain. The following morning the patient experienced shaking chills; the cough increased and each paroxysm intensified the low back pain. The patient complained of sore throat and of precordial and lower abdominal pain, and was admitted to the hospital. The temperature was 103°F. and the pulse and respirations were 128 and 18 per minute, respectively. The patient was acutely ill and in obvious distress due to repeated cough and sore throat. His face was erythematous, and blanched on application of pressure. The throat mucosa was red and edematous and numerous patches of hyperplastic lymphatic tissue were present. The left tympanum was inflamed but not bulging. The chest expansion was symmetric. No areas of dullness were demonstrated by percussion, but crepitant inspiratory and sibilant rales were audible at both bases anteriorly and posteriorly.

On January 11th the white blood cell count was 8,600/cu. mm. (neutrophils, 71; lymphocytes, 28; monocytes, 1). The throat culture showed no ab-

normality of flora. X-ray revealed peribronchial infiltration at the base of both lungs, most marked in the cardiophrenic angle on the right side.

The fever persisted continuously following admission until January 16th, after which sporadic elevations to 100°F. were recorded. On January 13th the patient's throat was intensely inflamed and edematous, and small white patches of exudate were present on the tonsils and the lymphoid tissue of the posterior pharynx. Coarse, as well as crepitant, rales were noted at both lung bases posteriorly. The cough was severe and non-productive. On January 14th non-tender enlargement of the submandibular lymph nodes was noted. The inflammation of the throat was maximal by January 15th, at which time patches of white exudate were present on both tonsils. Diminished breath sounds were heard over the middle chest posteriorly together with crepitant rales in both lungs. These findings were considered consistent with bilateral bronchiolitis and pneumonitis. The patient had no complaints following lysis of fever, but was restricted to bed for a prolonged period due to slow resolution of the pulmonary infiltration. The x-ray of February 8th showed partial resolution of pneumonitis at the left lung base and persistent bronchovascular shadows at the right cardiophrenic angle.

Comment: This patient illustrates a case of primary atypical pneumonia in which there was non-streptococcal exudative pharyngitis. Involvement of the conjunctivae (history), tympanic membranes and lymph nodes was also present along with the pharyngeal infection. Laboratory diagnosis of RI group infection in this patient was demonstrated by the recovery of type 7 virus from the throat washings and by the occurrence of significant increase in C-F and neutralizing antibody directed principally against type 7 virus. Cold and streptococcus MG agglutination tests were negative throughout the illness.

COMMENTS

The isolation of virus and the specific serologic results established the RI virus etiology in each of the forty-five patients included in the study. The fact that all eleven viruses recovered from patients were type 7 and that the patients developed neutralizing antibody primarily against this agent suggested that the majority of the cases in the epidemic were caused by type 7 virus. This was an unusual circumstance in view of the prevalence of three different types in other epidemics[6] and the finding (unpublished) that type 4 infections were common at Fort Dix shortly after the present cases occurred.

The patients who were studied all had acute respiratory illnesses severe enough to necessitate hospital care. The present report, therefore, defines the clinical picture in patients with the more severe form of the disease. Patients with mild disease[2,4] or inapparent infections[2,4] were not included in the present study.

The patients who were hospitalized with RI group infections manifested a basic syndrome of fever, pharyngitis and cough. This was associated with one or more of the following: conjunctivitis, rhinitis, catarrhal otitis media or externa, laryngitis, tracheobronchitis, bronchiolitis, pneumonitis and constitutional symptoms.

Based on the clinical findings, one may postulate the progress of events in RI virus infections to be as follows: The virus presumably gains entrance to the human host via the upper respiratory tract, i.e., through the nasal, pharyngeal or conjunctival mucosa. Following an incubation period of about five days, constitutional and respiratory symptoms become apparent. The characteristic pharyngeal lymphoid hyperplasia, which is present at onset of fever, may include superficial involvement of the lymphatic tissue giving rise to pinhead-sized patches of white exudate. Such areas of exudate usually increase in size, becoming confluent with neighboring patches. This peculiar inflammatory process, which is often accompanied by local lymphadenopathy, sometimes is confined to the posterior pharynx but more often progresses rapidly to involve the larynx, trachea, bronchi and bronchioles. In certain cases the bronchiolitis is sufficiently severe to cause pulmonary atelectasis and in others the process spreads further to involve the interstices of the lung resulting in a pneumonitis. The conjunctival involvement occurs concomitantly with the initial respiratory symptoms and is of little or no significance in the severity of the patient's illness. Convalescence from RI virus infection occurs by lysis of fever, diminution of the mucosal lymphatic hypertrophy, disappearance of the exudate, and a more gradual decrease in size of the cervical lymph nodes. Resolution of pneumonitis is less rapid and follows the pattern of other resolving viral pneumonias.

It is apparent from the present findings and previous reports[1–4,7–13] that quite a large segment of the respiratory illnesses of man are caused by viruses of the RI family. (Fig. 11.) This includes undifferentiated acute respiratory disease (ARD),[14,15] non-streptococcal exudative pharyngitis,[15] bronchitis resembling atypical pneumonia,[17] and a portion of the cases of primary atypical pneumonia[15–18] in which the

test for cold and streptococcus MG agglutinins remains negative. Primary atypical pneumonia cases in which the last-named tests become positive appear etiologically unrelated to the RI viruses and seem to be caused by a different agent.

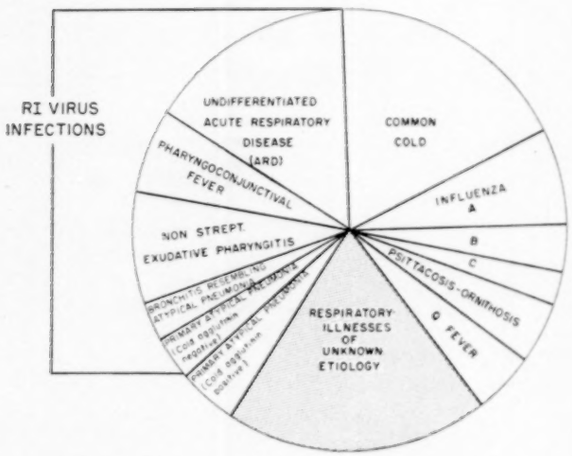

FIG. 11. Clinical syndromes and etiologic entities in common respiratory illnesses of man.

Also in this spectrum of diseases belongs the syndrome of pharyngoconjunctival fever described recently in civilian populations by Parrott and his associates,[7,10] and shown to be caused in these patients by type 3 APC or RI virus. The principal components of the latter illness, namely, fever, pharyngitis with or without exudate, rhinitis and frequent cervical or submandibular lymphadenopathy and conjunctiva inflammation, were prominent in the cases described in the present report, most if not all of which were caused by type 7 virus. However, there appeared to be differences in degree of involvement. Thus the duration and intensity of the febrile response was similar in both groups, but the pharyngitis in the present cases was of greater severity in relation to the amount of fever than among the cases studied by Parrott et al., and transient liver enlargement with tenderness was not present among the soldiers. The conjunctival change observed among the troops in the present investigation resembled that described by Parrott et al., particularly in that it involved both the palpebral and bulbar conjunctivas without affecting the corneas. The present cases differed, however, in that both eyes were always involved, while inflammation of one eye only was found commonly in Parrott's study. Furthermore, certain of the soldiers exhibited chemosis of the lids producing purulent drainage in one instance; this was not recorded among the civilian group. No attempt was made to recover virus from the eyes of the sick soldiers so that definitive information was lacking as to whether the conjunctivitis was indeed due to local viral infection, as shown in Parrott's cases.

These clinical entities of RI virus etiology fall within the more general syndrome of febrile catarrh described by Stuart-Harris and his associates in 1938.[27,28] They differ clinically from the "typical" common cold which is characterized by coryza, profuse watery nasal discharge and a mild febrile or afebrile clinical course of short duration. Additionally, patients exhibiting the typical common cold syndrome give negative results in serologic tests for RI infection.[1,12] It should be emphasized, also, that while the known viruses account for perhaps the majority of cases of acute respiratory illnesses, a sizeable portion of the total group of respiratory diseases still is of unknown etiology. This is the area in which further virologic investigations may bring about discoveries of new respiratory viruses.

Viruses of the RI family may be associated also with various non-respiratory illnesses in man. Thus Kjellen[29] has recovered agents of the group from cases of mesenteric lymphadenitis, and Huebner et al.[8] from a case of Letterer-Siwe disease. Neva and Enders[30] found an agent of the family in the stool of an infant with an illness resembling roseola infantum which proved to be a type 3 virus.[9] More recently, Jawetz et al.[31] recovered a virus of this group from cases of epidemic keratoconjunctivitis.

No attempt was made to evaluate the effect of terramycin in RI infections since this form of therapy was being employed in another study by others who made their patients available to us for investigation. However, the clinical impression was gained that the drug did not influence the course of the disease. The occasional patients who failed to receive the antibiotic or were unable to tolerate it presented a clinical course which resembled that of patients given the drug. Symptomatic therapy is indicated in RI disease. Steam inhalation reduces the intensity of the cough and this effect is enhanced by analgesic doses of codeine. Local anesthetics and opiates were not employed in the present patients but might be beneficial. Bedrest, aspirin and adequate fluid intake are usually sufficient to control the remaining symptoms.

SUMMARY

The clinical features in forty-five laboratory-proved cases of respiratory illness of RI virus etiology among hospitalized military personnel are described.

Type 7 RI virus was the sole or predominant agent among the cases studied. The patients manifested a basic syndrome of fever, pharyngitis and cough which was often accompanied by conjunctivitis, rhinitis, otitis, laryngitis, tracheobronchitis, bronchiolitis or pneumonitis, accompanied by constitutional symptoms.

These cases of RI etiology belong in the spectrum of syndromes designated as undifferentiated acute respiratory disease (ARD), pharyngoconjunctival fever, non-streptococcal exudative pharyngitis, bronchitis resembling atypical pneumonia and primary atypical pneumonia unassociated with the development of cold or streptococcus MG agglutinins. Collectively, the cases belong in the inclusive syndrome of febrile catarrh described by Stuart-Harris et al.

The "typical" common cold and primary atypical pneumonia associated with the development of cold and streptococcus MG agglutinins were not among the entities caused by the RI viruses.

Acknowledgments: The authors are indebted to Captains D. Mauriello, J. Trader, I. A. Schauffer and J. L. Redmond of Fort Dix for certain of the clinical, x-ray and laboratory observations, and to Dr. Harold B. Houser, Director, Laboratory on Housing and Illness, Sampson Air Force Base, New York, for performing the antistreptolysin tests.

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Coxsackie Viruses and "Virus-like" Diseases of the Adult*

A Three-year Study in a Contagious Disease Hospital

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INFECTION of man with viruses of the Coxsackie group may result in either of two clinical syndromes, herpangina or pleurodynia, which had been defined many years before the recent recognition of their etiologic agents.[1–3] Early studies of the relation of Coxsackie viruses to human disease were confounded by the frequent association of Coxsackie virus infection and poliomyelitis in some epidemics;[4,5] this in retrospect was probably a chance occurrence occasioned by the similar epidemiology of the two infections.[2,6] Most studies of Coxsackie virus infection have been either incidental to poliomyelitis investigations or directed specifically toward the etiology of pleurodynia or herpangina. The frequency of dual infections with poliomyelitis and Coxsackie viruses and the recovery of Coxsackie viruses from asymptomatic persons during epidemics[2] has engendered the suspicion that these viruses may be so ubiquitous in human materials as to be of questionable importance in human illnesses with which their presence is associated. The present report concerns a three-year study principally of adult patients admitted to a contagious disease hospital with various manifestations of febrile illness. It will be shown that in the population so selected recoveries of Coxsackie viruses were few and could reasonably be related to the coincident illnesses of patients in whom infection was demonstrated.

MATERIALS AND METHODS

Selection of Patients. During the period March 1, 1952 to March 1, 1955, patients hospitalized in the contagious unit of the Charity Hospital of Louisiana at New Orleans were selected for the present study, if on admission they were suspected of virus infections of the type not readily classified into known categories of disease. Such patients exhibited few if any localizing signs or symptoms, appeared unduly prostrated in proportion to the few physical signs evident, and usually manifested normal or low total leukocyte counts. (Table 1.) Most of these patients were more than twelve years of age. In addition, patients with signs of central nervous system disease or meningeal irritation associated with lymphocytic spinal fluid pleocytosis were also included as possible instances of "virus meningitis" or encephalitis. Certain cases of viral diseases of known etiology were deliberately included for study (Table 1) and retrospective evaluation of other cases has permitted their reclassification as diseases of bacterial etiology or non-infectious fever. Occasional patients from other hospitals in Louisiana were included in this study.

Fecal specimens and acute and convalescent phase serums were obtained from patients selected for study. Serums were stored at −30°C. in a mechanical deep freeze. Fecal specimens were stored as 10 per cent suspensions at −65°C. following homogenization in an electric mixer and sealing in glass. Throat washings, swabbings or tissues obtained from patients were also stored at −65°C.

Experimental Animals. Infant mice used were of the CFW strain and were less than two days old at the time of inoculation. Adult mice were males of the CFW strain, 16 to 20 gm. in weight.

Recovery of Virus. Two litters of infant mice were inoculated intraperitoneally with each 10 per cent aqueous extract of feces to which penicillin (1,000 units/cc.) and streptomycin (5 mg./cc.) had been added. The bacterial "sterility" of such preparations was equated with no growth at seventy-two hours following culture on rabbit blood agar. Mice were observed for tremors, paralysis or death for at least ten days after inoculation. Animals suspected of dis-

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TABLE I

CLINICAL ANALYSIS OF 125 PATIENTS FROM WHOM COXSACKIE VIRUS RECOVERY WAS ATTEMPTED FROM FECAL SPECIMENS

Clinical Category	No Virus Recovered	Virus Recovered
"Virus-like" disease (no localizing signs or symptoms)	24	..
Diseases of suspected viral etiology	24	..
Pharyngitis	6	
Enteritis	6	
Myalgia	9	
Lymphadenitis	3	
Virus diseases of known etiology	27	..
Paralytic poliomyelitis	15	
Hepatitis	7	
Varicella	2	
Mumps meningitis	3	
Lymphocytic meningitis	23	2
Encephalomyelitis	7	2
Encephalitis	4	1
Encephalitis (postexanthem)	3	1 (t.c.*)
Guillain-Barré syndrome	2	..
Diseases of bacterial etiology	8	..
Non-infectious fever	3	..
Disease of probable Coxsackie virus etiology	2	1
Pleurodynia	1	1

* t.c. = virus recovered only in tissue culture but later passages proved infant mouse pathogenic.

ease were killed by cervical fracture, skinned and eviscerated, homogenized in a mixer as a 10 per cent suspension of whole carcass and passed into infant mice by the intraperitoneal route; as many as three "blind" passages were carried out in some cases before a specimen was considered negative. Some specimens which induced equivocal disease were also inoculated into cortisone-injected adult mice.[7] The identity of agents isolated by this procedure was established by pathologic studies, negative lethal effects in adult mice and by specific neutralization with antiserums.*

Titration of Coxsackie Viruses and Neutralizing Antibody. Titrations of virus and antibody were usually effected by methods previously described.[8] In one

* Serums were generously supplied by Dr. Gilbert Dalldorf, whose laboratory assisted in the typing of our isolates.

TABLE II

SUMMARY OF VIRUS RECOVERY ATTEMPTS IN INFANT MICE FROM MATERIALS FROM 210 PATIENTS

	Specimens Tested	Virus Recovered	Coxsackie Virus	Other
Stool	140	4	4	..
Throat washing or swabbing	39	3	0	3*
Cerebrospinal fluid	25	0	0	0
Ocular washing	2	0	0	0
Vesicle fluid	1	0	0	0
Lymph node	2	0	0	0
Penile swab	1	0	0	0

* Herpes simplex virus recovered from patients in whom herpes simplex was suspected on basis of stomatitis or aphthous ulceration.

instance (Case 423) neutralizing antibody was demonstrated in the adult mouse by a modification of an ingenious method in which the specific group B virus lesion of pancreatic necrosis (as revealed by intravital staining) is prevented by antibody.[9]

Studies in Tissue Culture. Stools and spinal fluids from patients with lymphocytic meningitis or encephalitis were also inoculated into monkey kidney tissue culture in collaboration with Potash and Fox.[10] This technic effected the recovery of a Group A, type 9 Coxsackie virus (Case 382) not previously isolable in infant mice. It should be noted, however, that tissue culture proved inadequate for primary isolation of the Group A, type 9 virus recovered in infant mice from Case 311, despite the demonstrated tissue culture cytopathogenicity of this virus after mouse passage.

EXPERIMENTAL RESULTS

Recoveries of Virus. During the three years of the present study materials from 210 patients were inoculated into infant mice. A summary of attempts at viral isolation is presented in Table II. With the exception of three recoveries of herpes simplex virus from mouth or throat washings of patients suspected of herpes, only four viruses were recovered; all were from fecal specimens and were identified as of the Coxsackie group.

Clinical Analysis of Patients from Whom Coxsackie Viruses Were Not Recovered—Negative Isolation Attempts. Because fecal specimens afford the maximum opportunity for the demonstration of Coxsackie viruses,[2] "negative" recoveries of virus gain in significance if only patients from whom stool was obtained and studied are considered. In Table I the clinical patterns of 125 such patients are presented. The categories are self-explanatory. It should be emphasized that in each case exhaustive bacteriologic and serologic studies were made to prevent the inclusion

TABLE III

DATA ON PATIENTS FROM WHOM COXSACKIE VIRUSES WERE RECOVERED

Date	Case No.	Age	Clinical Diagnosis	Virus	Antibody	Source of Virus	Recovered in
4/2/53	209	5	Lymphocytic meningitis	A-7	*	Stool	Infant mice
8/4/53	311	7	Lymphocytic meningitis	A-9	†	Stool	Infant mice
6/11/54	382	17	Encephalitis	A-9	†	Stool	Tissue culture
8/12/54	407	23	Encephalitis	A-8	†	Stool	Infant mice
9/30/54	423	19	Pleurodynia	B-3	*	Stool	Infant mice

* Neutralizing antibody against homologous virus demonstrated in postinfection serum specimens.
† Increase in neutralizing antibody demonstrated.

of known bacterial or viral disease entities in those groups of cases designated as "virus-like" or of "suspected viral etiology." These studies included throat, stool and blood cultures as indicated, proteus OX-19 agglutinations, and agglutination tests for brucellosis, typhoid and paratyphoid fever (Salmonella A and B), and tests for heterophil antibody. Complement fixation tests for murine typhus* were performed on serums from forty patients.

It is apparent on inspection of Table I that few recoveries of virus were effected. None was demonstrable in patients with "virus" infections or clinically identified diseases. Recoveries of virus were effected only from four patients who manifested signs of central nervous system infection, and from one with pleurodynia. As will be pointed out, mere recovery of virus is inadequate evidence of an etiologic relationship of the virus to concurrent disease, yet the infrequency of virus recovery from this febrile segment of the population most liable to be infected suggests the probable importance of the positive isolation attempts.

Patients from Whom Coxsackie Viruses Were Recovered. A summary of pertinent data concerning patients from whom viruses were recovered is presented in Table III. Viruses were recovered from feces in infant mice in four instances, and in monkey kidney tissue culture from a fifth case in which mouse inoculation had previously been negative. All isolates but one were Group A viruses and were associated with meningitis or encephalitis. The only Group B virus recovered was associated with pleurodynia. Neutralizing antibody in high titer was demonstrated against the homologous viruses in postinfection serums of all patients, and in three patients increases in antibody were shown.

* Courtesy of Dr. Martha Everitt Jordan.

Case Reports of Patients from Whom Viruses Were Recovered. Graphic summaries of illnesses of patients yielding Coxsackie viruses are shown in Figures 1 to 5. Brief summaries follow:

CASE 209. This five year old white boy experienced the onset of restlessness and feverishness three days before hospitalization following a mild infection of the respiratory tract of two weeks' duration. The following day a severe frontal headache and transient blurring of vision developed. The next day anorexia, vomiting and irritability were manifest and a rectal temperature of 103°F. was noted. Lumbar puncture disclosed a pleocytosis of 189 cells/cu. mm. (Fig. 1) of which 76 per cent were lymphocytes. The patient was hospitalized the following morning with a rectal temperature of 103°F. Positive physical findings were marked irritability, slight back stiffness (but no nuchal rigidity) and questionable weakness of the left biceps. Laboratory data are recorded in part in Figure 1. Additional data included a normal urinalysis and chest x-ray and cerebrospinal fluid protein of 20 mg. per cent and glucose of 57 mg. per cent. The patient rapidly became afebrile. Examination on the second hospital day (fifth day of illness) disclosed continued irritability and back muscle spasm and a positive Kernig's sign. No muscle weakness was detected. Subsequently, the patient became completely asymptomatic and was discharged free of sequelae on the sixteenth hospital day.

A Group A, type 7 Coxsackie virus was recovered from feces on the seventh day of illness. Neutralizing antibodies to this virus were demonstrated in both acute and convalescent phase serums.

CASE 311.* Early in the morning on the first day of illness this seven year old white boy was awakened by a headache and pain in both ears. Shortly thereafter he vomited. In the afternoon the oral temperature was 101°F., and questionable stiffness of the neck was

* We are indebted to Dr. L. G. Horn of the Street Clinic, Vicksburg, Miss., for clinical information on this patient.

discerned by the patient's physician. At that time the boy was admitted to the hospital where a rectal temperature of 101°F. and minimal stiffness of the neck and back were found to be the only positive physical findings. Lumbar puncture disclosed a lymphocytic pleocytosis (Fig. 2), a spinal fluid protein

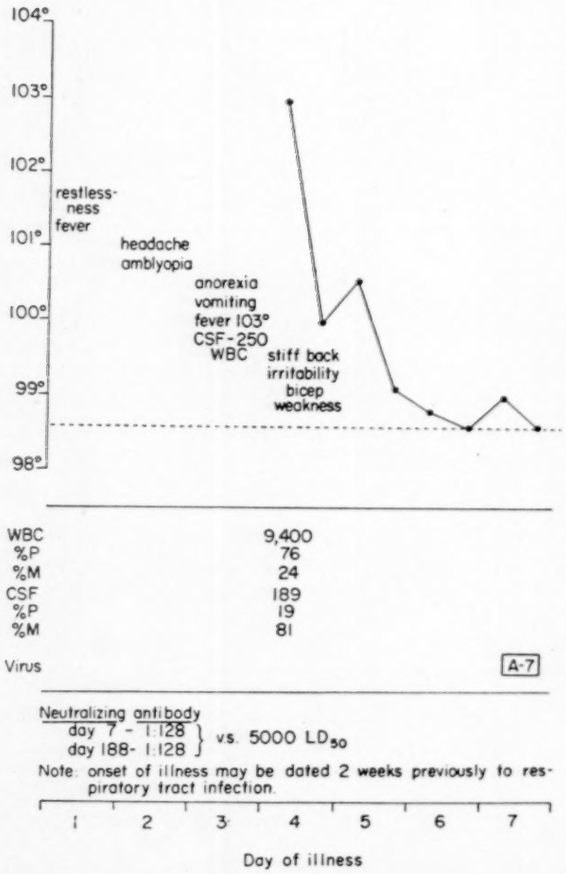

FIG. 1. Case 209, five year old white boy. Diagnosis: lymphocytic meningitis. The temperature scale is Fahrenheit. The maximum recorded temperature is indicated for each half day. The following abbreviations are used in all the figures: WBC, peripheral blood total leukocyte count; P, polymorphonuclear leukocyte; M, mononuclear leukocyte; E, eosinophil leukocyte; CSF, total leukocyte count of cerebrospinal fluid.

of 48 mg. per cent and glucose of 53 mg. per cent. Urinalysis gave negative results except for a trace of acetone. The total leukocyte count was 11,500/cu. mm. with 80 per cent polymorphonuclear and 20 per cent mononuclear leukocytes.

The patient became afebrile on the second day of illness but experienced a transient return of fever five days later. Subsequently his temperature remained normal. At the time of discharge from the hospital, thirteen days after the onset of illness, the patient was found to have questionable weakness of both quadriceps muscles and a slight ataxia. A complete muscle function test three weeks later revealed no weakness, spasm or muscular imbalance.

A Group A, type 9 Coxsackie virus was recovered from a stool specimen on the seventh day of illness, and study of paired serums (Fig. 2) demonstrated a rise in neutralizing antibody to the virus.

CASE 382. This seventeen year old white girl was hospitalized because of coma of one day's duration. She had been well until six days before admission (Fig. 3) when she noted generalized aching and malaise. Two days later a rash appeared which became generalized the following day and was identified by her physician as "measles." On the day the rash appeared the patient and her mother noted "kernels" (lymph nodes) behind her ears and inflammation of the gums. On the day of generalized rash, fever of 105°F. was recorded, and the patient complained of pain in the hands and feet. Tetracycline (achromycin®) therapy in unknown dosage was instituted. The following day (fifth day of illness) the patient became afebrile and the rash "faded." The succeeding day was asymptomatic except for continued pain in the extremities. On the morning of hospital admission the patient suddenly vomited about one-half cup of watery red liquid alleged to be blood; she subsequently lapsed into stupor after a period of marked confusion and disorientation.

On admission to the hospital the patient was found to have a rectal temperature of 103.2°F., a tachycardia of 150 per minute and clouded consciousness described as semi-coma. She was restless and unresponsive to commands. The skin showed no evidence of rash but a malar flush was noted. Positive findings included conjunctival injection and absence of all tendon reflexes save for left knee and ankle jerks. Laboratory studies showed minimal leukocytosis (Fig. 3) and the presence of eight erythrocytes and one polymorphonuclear cell in a clear spinal fluid. The Pandy test was negative in the spinal fluid; the glucose was 85 mg. per cent.

On the day after admission re-examination disclosed the following physical signs: (1) bilateral blurring of the nasal margin of the optic discs; (2) asynchronous ocular movements; (3) flaccid paralysis of the left arm; (4) spasticity and paresis of the right leg associated with an extensor plantar response on the right and an absence of the right knee jerk; (5) cutaneous abdominal reflexes were not elicited and (6) the patient responded only to noxious stimuli. Subsequently the patient's temperature dropped abruptly and she became afebrile and fully conscious the third hospital day. She was discharged without any evidence of sequelae six days later.

A Group A, type 9 Coxsackie virus was recovered from a fecal specimen obtained on the thirteenth day of illness. A rise in serum neutralizing antibody was

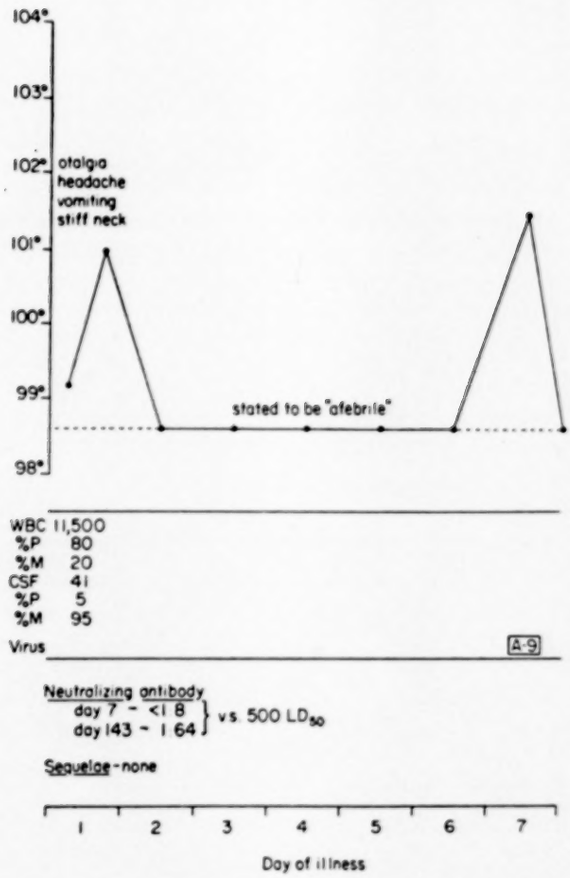

FIG. 2. Case 311, seven year old white boy. Diagnosis: lymphocytic meningitis.

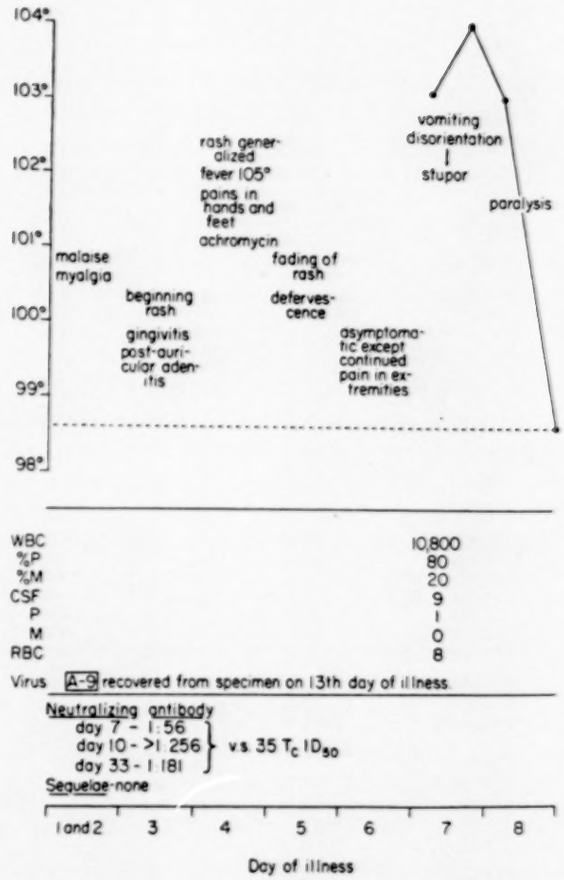

FIG. 3. Case 382, seventeen year old white girl. Diagnosis: encephalitis, postrubella.

demonstrated in monkey kidney tissue cultures as indicated in Figure 3.

CASE 407.* This twenty-three year old white man suffered moderately severe retro-orbital and generalized headaches during the week prior to admission. The day before admission he noted "numb spots" on his hands and feet while at a movie. That night he retired to bed about 10:30 P.M.; his wife noted that he was restless. Five hours later he awakened crying uncontrollably. He appeared not to recognize members of his family and attempted to leave the house. He was coaxed back to bed but again arose and wandered aimlessly about. For about one hour he was apparently unable to speak, and thereafter vocalizing resulted in jargon. When seen by his physician on the morning of admission, the patient was able to utter coherent phrases but occasionally regressed to unintelligibility. He was oriented as to place. Neurologic examinations at his home and later that morning at the hospital were not remarkable. The patient complained of slight neck stiffness but nuchal rigidity was not noted on physical examination. Positive physical findings were not elicited, except for a rectal temperature of 100°F. Initial diagnostic impressions included "conversion hysteria" and "fugue state."

The total leukocyte count was not elevated. (Fig. 4.) Lumbar puncture revealed clear fluid under increased pressure (300 mm. H_2O); 105 cells/cu. mm., all mononuclear in type were counted; the spinal fluid protein concentration was 56 mg. per cent.

The patient's motor aphasia and disturbed sensorium cleared within a few hours after hospitalization, although slight slurring of speech and headache continued throughout the day. Neither undue restlessness nor somnolence was noted. On the day after admission an electroencephalogram demonstrated grossly abnormal rhythm with paroxysms of high voltage theta and delta waves. Lumbar puncture was repeated on the fifth day of illness and demonstrated forty-one mononuclear cells/cu. mm. Total spinal fluid protein was 51 mg. per cent with a "slightly positive" reaction to the Pandy test. The spinal fluid Wassermann reaction was negative.

When seen ten days later (fifteen days after onset

* We are indebted to Dr. W. S. Culpepper of the Ochsner Clinic for clinical information on this patient.

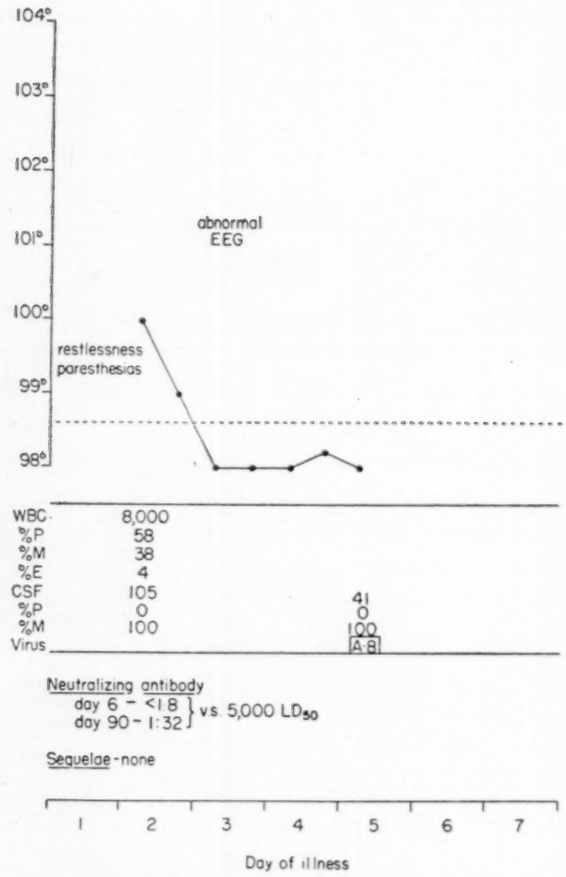

FIG. 4. Case 407, twenty-three year old white man. Diagnosis: encephalitis.

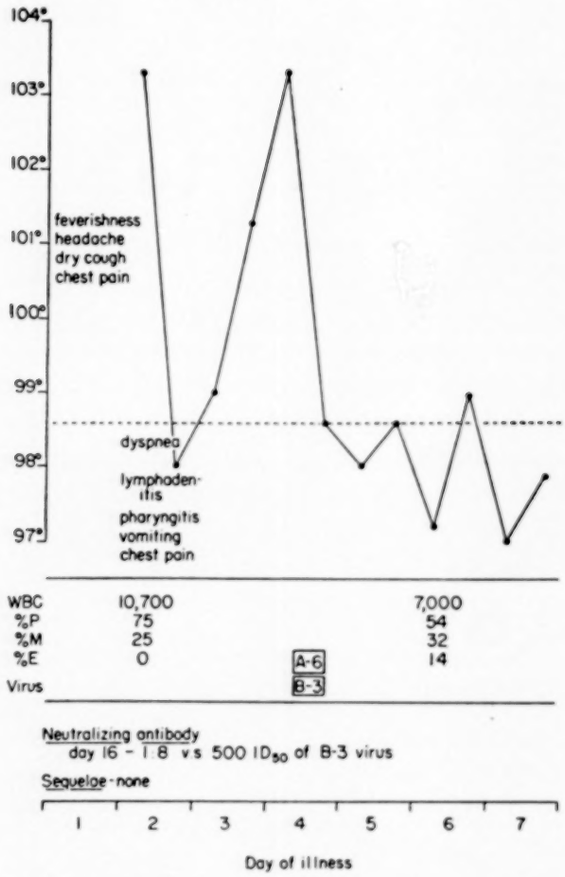

FIG. 5. Case 423, nineteen year old white man. Diagnosis: pleurodynia.

of illness) after convalescence at home, the patient was found to be in good health and free of discernible sequelae. From a fecal specimen obtained on the fifth day of illness a Group A, type 8 Coxsackie virus was recovered. Acute phase serum in a dilution of 1:8 failed to neutralize this virus, while 50 per cent neutralization was effected by a 1:32 dilution of serum obtained three months later. (Fig. 4.)

CASE 423. This nineteen year old white man was well until the day prior to admission when he experienced the onset of increasingly severe frontal headache and a dry cough. On this day he suffered severe brief episodes of stabbing precordial pain worsened by deep respiration. On admission physical examination revealed an oral temperature of 103.6°F., lethargy, mild pharyngeal injection and enlarged tender lymph nodes in the anterior and posterior cervical chains, axillary, inguinal and epitrochlear regions. Minimal leukocytosis (Fig. 5) was the only positive laboratory finding.

The patient's temperature dropped precipitously on the first hospital day but rose again without interruption to above 103°F. on the morning of the third day after admission. By evening the patient had become afebrile and remained so thereafter. During the secondary temperature rise of the second and third hospital days the patient complained of a left-sided aching pain in his chest accentuated by movement and deep breathing. This disappeared coincident with defervesence. On the sixth day of illness (Fig. 5) a total leukocyte count was normal and a differential count revealed an eosinophilia of 14 per cent.

A fecal specimen obtained on the fourth day of illness induced paralytic disease in infant mice which was not preventable by either acute phase or convalescent serum of the patient when as little as 50 ID_{50} of virus was used. However, pancreatic necrosis and death of adult mice was induced with the fecal isolate and cortisone, and this effect was neutralized with convalescent serum. This suggestion of the possibility of multiple agents in the stool isolate—only one pathogenic for the adult mouse—was confirmed by the identification of two viruses, Group B, type 3, and Group A, type 6. Only the Group B virus

was pathogenic for adult mice and was neutralized by the patient's convalescent serum. Acute phase serum had been exhausted prior to separation of the two viruses so that a rise in antibody titer could not be demonstrated. That the recovery of the A-6 virus was not the result of laboratory contamination is suggested by (1) the re-isolation of both viruses from the original fecal specimen, and (2) the fact that A-6 virus was not known to have been present in this laboratory prior to this isolation. The absence of demonstrable antibody response to the A-6 agent by the patient casts doubt on the probability of his having suffered actual infection with this virus and equivocates its relation to his disease. However, follow-up was inadequate to have excluded the appearance of antibody late in convalescence (i.e., after sixteen days).

Incidence of Recoveries of Coxsackie Viruses from Fecal Specimens of Pediatric Patients. It has been rightly emphasized by Huebner and his associates[2] that assessment of the etiologic relationship of Coxsackie virus infection to human disease requires inquiry into the incidence of infection of control groups of undiseased persons. Although the very infrequency of positive isolations in the present study strengthens the "significance" of each isolation, the fact that most of the patients studied were adult (i.e., more than twelve years of age) raised the question that a much higher incidence of infection might be occurring in children in the community in view of the greater frequency of Group A infections in childhood.[2] If this were true, the importance of occasional recoveries of virus from adults would be lessened. Accordingly, fecal specimens from fifty-eight randomly selected patients admitted to the pediatric contagious services of Charity Hospital between September 20 and October 16, 1954, were tested for the presence of Coxsackie viruses by infant mouse inoculation. This time-period represents late summer in Louisiana and marked the end of the summer which had yielded virus isolations in adults. (Table III.) The children studied were all febrile and therefore constituted a harsh challenge as a control group as it would be expected that ill children would be more liable to be infected with Group A viruses because of the high attack rate of clinical disease.

From only two of fifty-eight children were viruses recovered (3.5 per cent): a Group A, type 4 virus, and an untyped Group A strain. It is probable, therefore, that during the period of sampling, and earlier as well (because of the persistence of the fecal carrier state[2]), Coxsackie virus infections were not epidemic in New Orleans. It is of interest that specific diagnoses had not been made in either of the two children who yielded viruses, and that their clinical records were compatible with a diagnosis of herpangina.

Failure to Demonstrate Infection with Known Neurotropic Agents in Patients from Whom Coxsackie Viruses Were Recovered. Serologic tests for the detection of increased antibody* against the viruses of mumps, eastern equine encephalitis, lymphocytic choriomeningitis and herpes simplex or poliomyelitis viruses types 1, 2 and 3 were negative in Cases 209, 382 and 407 from which Coxsackie viruses had been recovered. Complement fixation or capillary agglutination tests with three types of leptospirae† (L. icterohaemorrhagiae, L. canicola and L. pomona) also failed to show evidence of infection in these cases. Furthermore, attempts to recover poliomyelitis viruses from fecal specimens in monkey kidney tissue culture were fruitless. In Case 311 a shortage of serum permitted the exclusion only of lymphocytic choriomeningitis virus infection by serologic tests; poliomyelitis viruses were not recovered in tissue culture.

Such negative information is subject to guarded interpretation as being truly exclusive but enhances the significance of the Coxsackie virus isolations.

DISCUSSION

Within the temporal and geographic limits defined for the present study, it has been demonstrated that infection of adults with Coxsackie viruses was an infrequent occurrence. When such infection did occur, it was associated with encephalitis for which other etiology could not be found, or with pleurodynia—now well established as a manifestation of Group B Coxsackie virus infection. No case of ill defined "virus-like" disease could be attributed to infection with a Coxsackie virus. It is possible that the situation might differ if Group B infections were prevalent in a community, as the diverse clinical manifestations of such infections has been stressed.[8]

The isolated instance of pleurodynia in the present study is of considerable interest as it

* Details of the serologic methods employed are presented elsewhere.[10]

† Leptospiral studies were performed by Dr. Joseph H. Schubert through arrangement with Dr. Donald S. Martin of the Communicable Disease Center, Chamblee Ga.

demonstrates that sporadic interepidemic infections may occur and suggests that such infections may constitute a human reservoir of infection, as has been postulated for interepidemic cases of influenza.[11] The recovery of two different viruses from the pleurodynia patient is illustrative of the difficulties encountered in assessing the significance of Coxsackie virus isolations. Were it not for the previous identification of the Group B, type 3 virus with pleurodynia outbreaks[12,13] and failure to demonstrate A-6 antibody in the patient, the Group A, type 6 agent might be held equally culpable in the genesis of the illness.

Infection of man with Group B Coxsackie viruses may clearly result in lymphocytic meningitis[13–15] with or without concomitant pleurodynia. Group A viruses, although related to the childhood disease herpangina[16] and frequently isolated in association with poliomyelitis,[5] have not thus far been implicated unequivocally in central nervous system disease. Further, Group A viruses differ from those of Group B in that they do not induce central nervous system lesions in mice. It is notable, however, that only one of the three Group A strains recovered in the present study (type 8) has been etiologically related to herpangina, and that the role of the other types (7 and 9) in human disease is in doubt.[16] Although definitive proof of the relation of viruses to central nervous system disease requires their demonstration in the spinal fluid or tissues of the host, the possible etiologic role of Group A Coxsackie viruses in the present cases is suggested by the following facts: (1) The transient and bizarre clinical manifestations in the two adult cases of encephalitis were not characteristic of known types of viral encephalitis. (2) During a time of non-epidemic prevalence, viruses were recovered from patients coincident with or just subsequent to central nervous system symptomatology. (3) Antibodies against the viruses recovered were demonstrated in serums obtained following illness, and in three cases rises in antibody were demonstrated.* (4) Attempts to demonstrate infection with the more common, known causes of meningoencephalitis including poliomyelitis virus were negative.

The possibility that Group A Coxsackie viruses may be implicated in postexanthem types of encephalomyelitis (Case 382) must be advanced with considerable caution in view of the virtual impossibility of proving that the patient concerned had rubella. It is possible that the exanthem in this patient was a previously undescribed manifestation of infection with Group A, type 9 Coxsackie virus.

The greater severity of the disease noted in the older patients is in accord with the observation that the clinical course of many virus infections increases in severity after childhood. Just as infection with poliomyelitis[17] and herpes simplex[18] viruses may induce different manifestations of disease in adults and children, the present study suggests that adults who have escaped childhood infections may suffer more dramatic illnesses in later encounters with the Group A viruses (Case 407). It is notable that this latter patient would not have been considered to have had an infectious disease had spinal fluid pleocytosis not been remarked. Such patients are seldom subjected to virologic investigation.

It is evident that definitive determination of the clinical patterns of Coxsackie virus infections will be dependent on further case reports in which non-epidemic disease is studied with emphasis on clinical analysis, and in which specific typing of viruses is effected and antibody response demonstrated.

* The presence of antibody prior to or coincident with the isolation of virus is evidence against hospital "pick-up" of virus but leaves unanswered the question of whether clinically inapparent infections might have occurred prior to the illnesses studied. Antibody response following Group A virus infections is prompt, however, and antibody present on day 7 of illness might indeed be the result of that illness.

SUMMARY

1. Coxsackie viruses were not recovered from adult patients hospitalized for either "virus-like" or etiologically defined febrile diseases during a three-year study in Louisiana.

2. Group A Coxsackie viruses were recovered from four instances of acute central nervous system disease, including a patient with a post-exanthem encephalitis. The possible etiologic role of these viruses in the genesis of central nervous system infections is discussed.

3. A Group B, type 3 Coxsackie virus was recovered from a sporadic case of pleurodynia.

4. It is concluded that Coxsackie viruses are not important incitants of interepidemic "virus-like" disease in adults. Viruses of Group A may have a hitherto unappreciated role in disease manifested by central nervous system symptomatology.

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Outbreak of Unusual Form of Pneumonia at Camp Gruber, Oklahoma, in 1944

*Follow-up Studies Implicating Histoplasma Capsulatum as the Etiologic Agent**

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An outbreak of an unusual form of pneumonia occurred at Camp Gruber, Oklahoma, in 1944.[1] The outbreak appeared to have a common source, the attack rate was high and most of the patients revealed extensive and protracted pulmonary infiltration. The present paper will review the outstanding clinical and epidemiologic features of the epidemic and the various follow-up studies which have already been reported.[1-8] Finally, the results of a comprehensive follow-up study will be presented. In retrospect, it now seems clear that the epidemic was caused by Histoplasma capsulatum.

REVIEW OF EPIDEMIC

The epidemic was recognized in late March and early April 1944 when twenty-seven patients who had an unusual form of pneumonia were admitted to the Station Hospital at Camp Gruber, Oklahoma. The patients presented a distinct clinical syndrome differing from the common forms of pneumonia. All of them had entered an abandoned storm cellar during field maneuvers, approximately twelve days prior to onset of the disease. Epidemiologic investigations of the outbreak indicated that it had been caused by a specific agent acquired from a common source. Etiologic studies made during the outbreak and for several months thereafter failed to reveal the cause.

The illnesses were characterized by rather sudden onset of predominantly constitutional symptoms, substernal pain and constriction in the chest.[1,3,4] Symptoms of upper respiratory tract infection were notably minimal or absent, and cough was mild or non-existent early in the course.

Most of the patients were severely ill for a period of from two to four weeks. Fever was remittent and reached levels of 104° to 106°F. on occasion. Nearly all of the patients had cough but it was usually mild and productive of only small amounts of mucopurulent sputum. Substernal pain, constricting and pressing, was the outstanding symptom. Deep breathing commonly induced pain and coughing. Minimal physical signs were present over the lungs early in the illness. Later scattered areas of slight dullness, associated with suppressed breathing sounds or rales, were found. The scarcity and minimal nature of the physical signs over the lungs were impressive in contrast to the widespread roentgenographic changes. In most cases chest films revealed extensive mottled infiltrations of a uniform pattern. Multiple lesions, varying from 1.0 to 20 mm. in diameter, were scattered diffusely and symmetrically throughout both lung fields, although fewer lesions were noted in the extreme apices and bases. The lesions appeared to be larger and more variable in size than those of miliary tuberculosis. Large areas of consolida-

* From the Department of Microbiology, University of Virginia, the Communicable Disease Center, Public Health Service, United States Department of Health, Education and Welfare, and the Departments of Medicine and Preventive Medicine, School of Medicine, Western Reserve University. This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, and was supported in part by the Office of The Surgeon General, Department of the Army.

tion were not present. In most cases the hilar lymph nodes were enlarged, and in some of the mild cases hilar enlargement was the only finding. These changes in the lungs were detectable a few days after onset of illness and reached maximum intensity within ten or twelve days. No clinical features which suggested involvement of areas other than the lungs were noted. Laboratory studies revealed little of significance except for an increased erythrocyte sedimentation rate during the acute phase.

Improvement began during the third or fourth week after onset and was gradual. A few patients continued to have fever for six weeks. The pulmonary lesions remained static for about two months, at which time slow resolution began. As the lesions decreased in size they became discrete and fibrotic and by six months the lung fields showed diffuse fine fibrosis. The hilar glands decreased in size parallel with regression of the pulmonary lesions. As will be emphasized in the follow-up studies, recovery was slow and often incomplete. At the end of seven and one-half months, twenty-one of the patients had required release from the armed services as a result of the illness and were still complaining of severe fatigue, weakness and pain in the thorax following mild exercise.

The epidemiologic data revealed several pertinent facts. The abandoned storm cellar was situated near the outer limits of the training area. It was dusty. In many places the boards and rafters were decaying and heavy growths of fungi were seen on the walls. The men stated that blankets were used on the ground and were shaken in the cellar. Two attempts to build small fires were made.

First use of the storm cellar was on the night of March 16, 1944, during blackout maneuvers when thirty-one men entered it. Subsequently, one man entered the cellar on March 18 and eight men on March 24; on May 17, two persons inspected the cellar to gather specimens for etiologic studies. Exposure time varied from a few minutes to several hours. No other persons are known to have entered the cellar.

Of these forty-two persons thirty-one are known to have had the disease (twenty-seven were hospitalized), an attack rate of 73.9 per cent; of the remainder four had signs and symptoms suggestive of the disease, four had no illness and three were not available for study. The time from exposure in the cellar to onset of symptoms averaged approximately twelve days, but ranged from eight to eighteen days. In nine cases the period was ten days.

The unique feature of this outbreak, then, was the limitation of illness to persons who had been in the cellar. A suggestive correlation was noted between the length of exposure and the severity of illness. Men who were continuously and intimately exposed to the patients, but who had not been in the cellar themselves, did not become ill.

In 1943 illnesses indistinguishable clinically or roentgenographically from the present ones occurred at Camp Gruber[1,4] and at Camp Crowder, Missouri.[9] At Camp Gruber, five men were admitted to the hospital in late February. In none of the case histories is there any record of experiences in the cellar in question. At Camp Crowder, among forty cases reported as primary atypical pneumonia, at least four were similar to the illnesses at Camp Gruber. All four of these men had cleaned abandoned houses, barns and chicken coops.

A detailed account of the many etiologic studies[1,2] made, both during the present epidemic and in the ensuing months, will not be presented here. Such studies included a search for evidence of primary atypical pneumonia, psittacosis, lymphocytic choriomeningitis, Q fever, leptospirosis, trichinosis, tularemia, brucellosis, coccidioidomycosis, moniliasis and histoplasmosis. Candida albicans was isolated from the sputum of many of the patients but the role of this organism was considered questionable, because of the lack of supportive evidence. H. capsulatum was not found either in specimens of sputum or in dust from the cellar and the area immediately surrounding it, but special search for this organism was not made at that time.

FOLLOW-UP STUDIES

Preceding and concurrent with the comprehensive follow-up studies which form the basis of the present report, several events and published reports have lent growing support to the idea that the epidemic in 1944 was due to H. capsulatum.

In 1944 Smith[10] performed complement-fixation and precipitin tests for histoplasmosis and coccidioidomycosis with serums from most of the patients from Camp Gruber, employing control serums from patients in whom the existence of these two diseases had been proved. Serums from ten to twelve patients from Camp Gruber showed antibody titers for histoplasmosis as

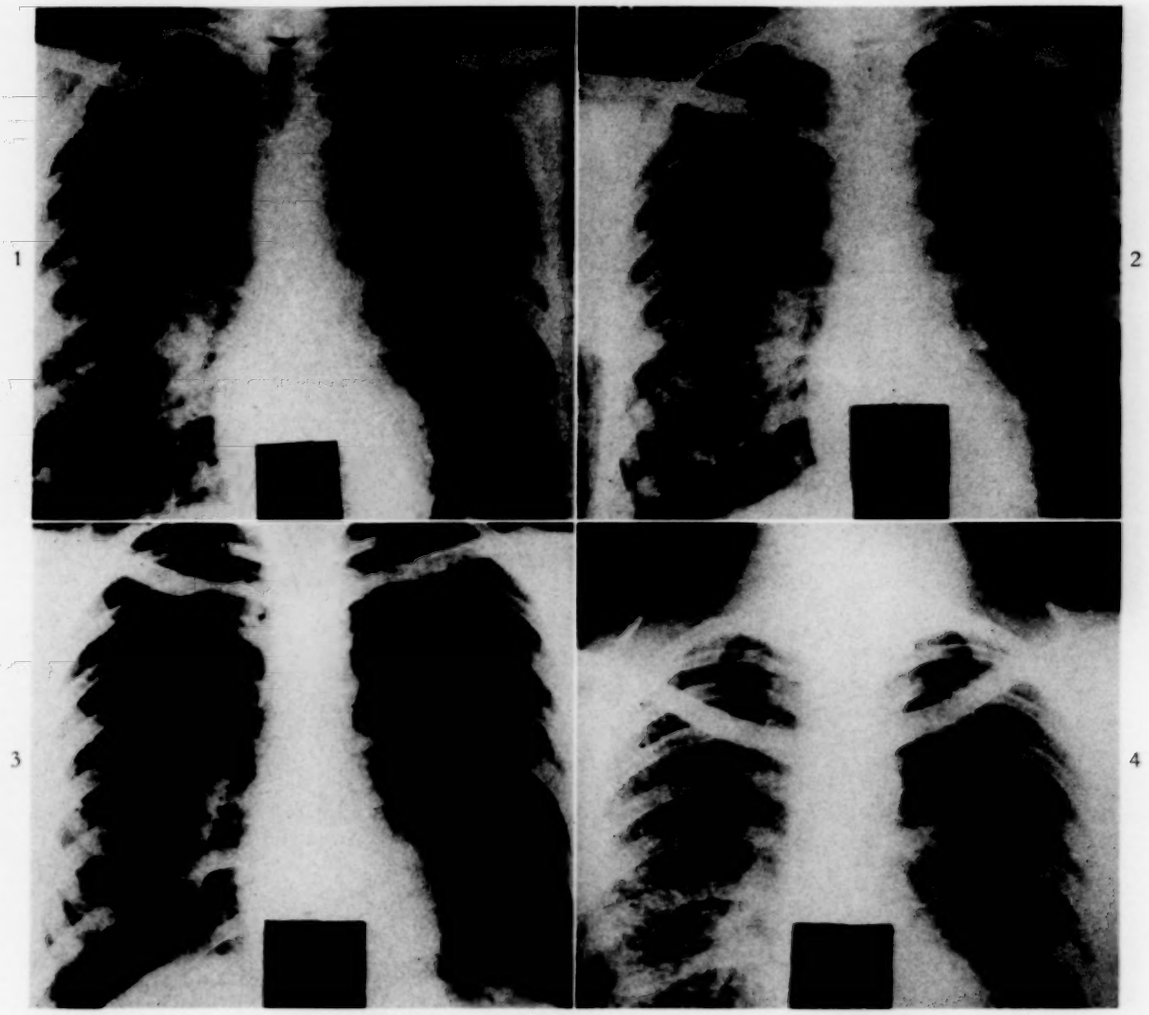
high as those of the control serums or higher. In addition, low titers of antibodies for coccidioidomycosis were demonstrated in two patients. In subsequent tests difficulty was experienced in obtaining histoplasma antigen that was free from anticomplementary action. This difficulty led both Dr. Smith and the Commission on Acute Respiratory Diseases to discount the results of the first set of tests. Dr. Smith pointed out, however, that the irregular coccidioidal complement fixation results with these serums did not coincide with the few coccidioidin skin reactions observed in tests performed on the patients, and also that the serums showed much greater fixation with histoplasma antigen than with coccidioidal antigen. He concluded, "It is conceivable that some other infection was acquired which has antigenic factors common both to coccidioides and histoplasma. If so, it is apparently more akin to the latter than the former."

Further interest in the Camp Gruber epidemic arose when numerous cases of miliary pulmonary calcification were noted in school children in a survey in Kansas City in 1945.[11] Among these children several active cases with disseminated pulmonary infiltration in the acute stage were encountered. In all of these cases skin tests gave a positive reaction to histoplasmin but gave a negative reaction to tuberculin. From one of these disseminated cases in the active stage, H. capsulatum was isolated. These data indicate that infection with this fungus could cause disseminated pulmonary infiltration, the end result of which was miliary calcification of the type known at that time as "healed miliary tuberculosis." The chest films and description of the illnesses that occurred at Camp Gruber seemed to be compatible with this possibility.

Three members of the Commission on Acute Respiratory Diseases had gone to Camp Gruber in May 1944 to study the outbreak[2] and had obtained serum specimens from patients and control subjects. These specimens were kept in storage for possible future study. The serums were collected approximately two months after onset of the illness, however, and should be considered as "convalescent phase" and not "acute phase" specimens. In 1947 Dr. Smith provided a histoplasma antigen suitable for complement fixation tests and a control rabbit antiserum. The results of these complement fixation tests with histoplasma antigen have been reported elsewhere[4] and will only be summarized here. The findings from the serums of patients having the unusual pulmonary disease differed in several respects from results of similar tests on serums of the control subjects of several groups. All of the serums from the patients showed detectable antibody levels whereas serums giving negative results were present in the control patients even if the number of persons in each group was small. Titers of patients' serums, as a group, were definitely higher than those of the control subjects. Finally, serial serums from one patient showed a progressive drop in titer. Although these serologic results were not conclusive, they suggested that the unusual disease was pulmonary histoplasmosis. More definitive serologic evidence would have required acute-phase serum specimens from the patients, but such serums were not available.

Two reports appearing in 1952 afforded further strong support for the idea that the epidemic at Camp Gruber in 1944 was caused by H. capsulatum.[5,6] According to one report, H. capsulatum was found, both by direct isolation and by means of animal inoculation,[8] in soil obtained from the storm cellar in which the soldiers were exposed in 1944.[5] The other report concerned a follow-up study made in 1950 of one of the patients who had diffuse pulmonary infiltration during the epidemic in 1944.[6] Roentgenologic examination of this person's chest revealed miliary and somewhat larger sized calcified nodules scattered diffusely throughout both lung fields. A skin test with histoplasmin gave a strongly positive reaction, skin tests with coccidioidin and tuberculin gave negative results. A complement fixation test for histoplasmosis of the serum in a dilution of 1 to 140 gave positive results.

Finally, in 1954 serologic tests were performed on serums collected in 1944 at Camp Gruber, Oklahoma, and in 1951 and 1952 in connection with the follow-up studies reported here.[7] Serums were available from patients and from persons in certain control groups. Serologic results with H. capsulatum antigens, employing the complement fixation and precipitation technics, revealed that antibodies were present in the serum from each of the men involved in the pneumonitis outbreak. Such antibodies either were not present or were present to a lesser degree in the subjects in the control groups. Since these data are incorporated into the results to be reported, they will not be discussed here.



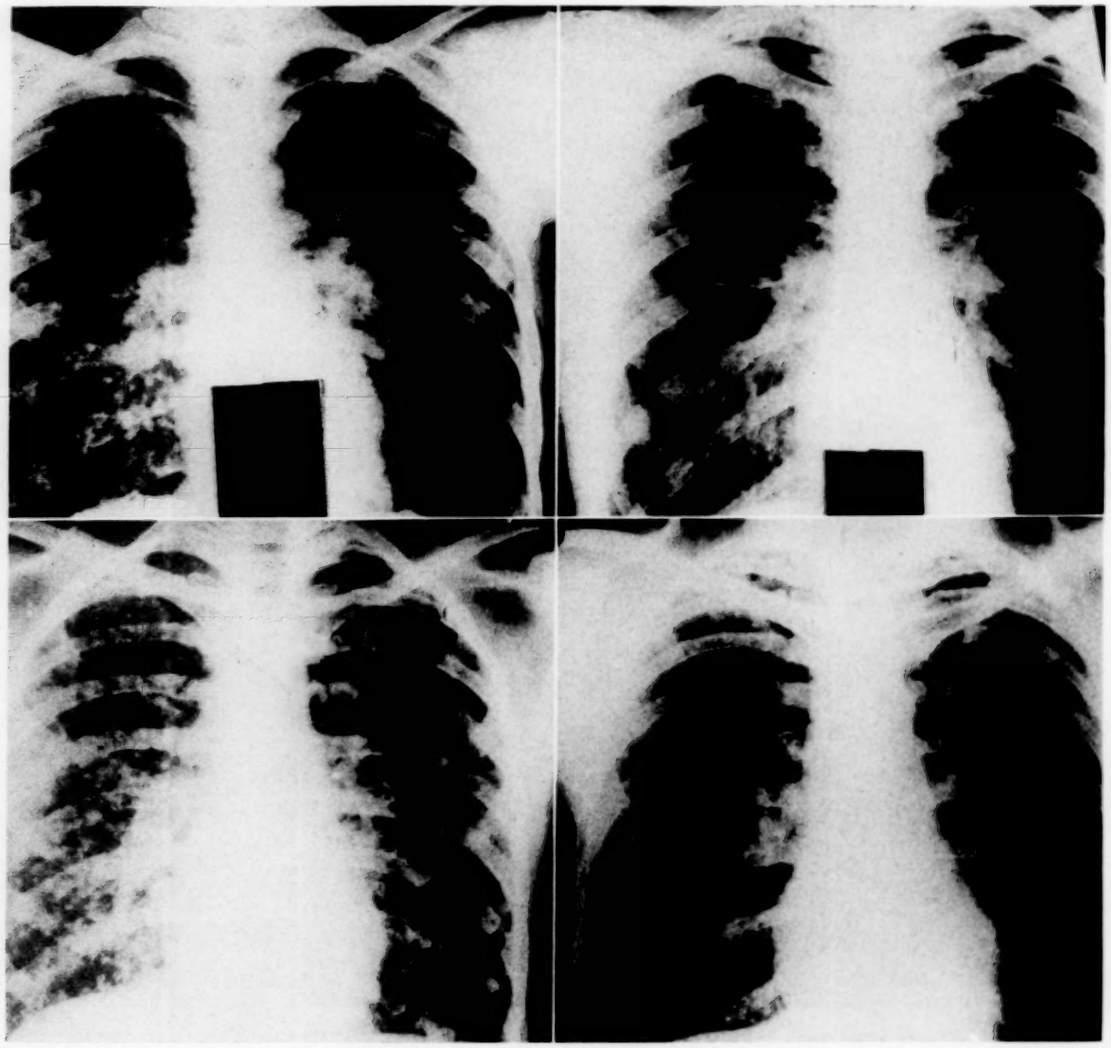
FIGS. 1 to 4. Note disseminated lesions. Figures 1 to 3 show the chronic character of the pulmonary lesions which are still evident after six and a half months. Figure 4 shows healing by miliary calcification six years later.

PRESENT STUDY

The follow-up group consisted of thirty-seven men. The group included men involved in the epidemic and certain control subjects to be noted. The studies were done without definitive knowledge of which men were control subjects and which were patients. The men were in twenty-one states and Hawaii and several were still in the Army stationed in Germany and Japan. When all were located, follow-up examinations were performed, either by official agencies in the area or by family physicians of the patients.

The soldiers were divided into three categories. Group A: This group consisted of twenty-six of the twenty-seven men who were hospitalized during the outbreak in March 1944. One man could not be located; most of these men lived on the eastern seaboard. Group B: The three men in this group were persons in whom roentgenograms of the chest had been found to reveal characteristic widespread pulmonary infiltration but in whom the illnesses had occurred at Camp Gruber in 1943, one year before the outbreak occurred. Group C: This category was comprised of eight members who belonged to the same military organizations as the men involved in the epidemic but who had remained well. Data obtained subsequently revealed that three of these eight men had entered the storm cellar in 1944. One man estimated that he had been in the cellar for only thirty seconds.

Information obtained in the follow-up study included a brief case history, the length of time



FIGS. 5 to 8. Figure 5 shows disseminated pulmonary infiltration with bilateral hilar lymphadenopathy in 1944. Figure 6 shows miliary calcification in 1951. Figure 7 shows acute lesions in 1944, while Figure 8 shows disseminated calcification in 1952.

hospitalized at Camp Gruber, a statement concerning discharge from the Army because of illness, whether or not veterans' compensation was being received and, finally, whether or not symptoms referable to the lungs were still present. Skin tests with histoplasmin (H-42-1:100), blastomycin (B7-1:1000), coccidioidin (29-31-1:100), and tuberculin (PPD-S .0001 mg.) were performed and a 14 by 17 inch roentgenogram of the chest was obtained. A serum specimen was obtained from each man.

The serums were tested in two laboratories. At the Communicable Disease Center laboratories complement fixation tests were performed using histoplasmin as antigen, and in the Rocky Mountain Laboratories of the National Institutes of Health Dr. Samuel Salvin employed whole yeast-phase cells of H. capsulatum as antigen for complement fixation and histoplasmin as antigen in precipitin tests. Results reported here include the data from both laboratories.

Results. Follow-up studies of the persons in Group A, which consisted of the men who were hospitalized at Camp Gruber, were complete except for skin tests on one person and serologic studies on two persons. (Table I.) Of the twenty-six men studied, eighteen had been discharged from the Army because of illness following exposure in the storm cellar. Thirteen men are now receiving veterans' compensation and fifteen reported the persistence of pulmonary

TABLE 1

CAMP GRUBER FOLLOW-UP STUDIES

GROUP A: DEFINITE CASES RELATED TO STORM CELLAR, MARCH 1944

Major Residence	Hospitalization, Camp Gruber		Veterans' Compensation	Status at Time of Follow-up						
	Duration (months)	Symptoms at Discharge		Symptoms	Skin Tests*				Serology	Pulmonary Infiltration
					T	H	B	C		
Mass.	8	+	−	+	−	+	−	−	±	Miliary
Mass.	9	+	+	+	+	+	−	−	±	Miliary
N. Y.	1	−	−	−	+	+	−	−	±	? Miliary
Pa.	5	+	..	+	−	+	+	−	+	Miliary
N. Y.	8	+	−	−	−	+	+	−	±	Other calcifications
Pa.	7	..	..	+	+	+	−	−	+	Miliary
N. Y.	7	+	+	−	..	..	..	..	..	Miliary
N. C.	9	+	+	+	−	+	−	−	±	Miliary
Va.	8	+	+	−	−	+	−	+	−	Miliary
Mich.	6	−	−	−	+	+	−	−	..	.....
Ill.	2	+	..	..	−	+	−	−	−	Miliary
Miss.	7	+	+	+	+	+	−	−	±	Miliary
Ga.-Fla.	7½	+	−	+	−	+	−	−	±	? Miliary
Ga.	9	+	+	−	−	+	−	−	+	Miliary
Texas	9	+	+	+	+	+	−	−	−	Miliary
La.	9	+	+	+	−	+	−	−	−	Miliary
Ind.	9	+	+	+	−	+	−	−	+	Multiple calcifications
Hawaii	6	−	−	−	−	+	−	−	±	Old pleurisy
Ala.	5	−	−	+	−	+	−	−	−	Miliary
N. J.	3	−	−	−	−	+	+	+	−	Miliary
N. J.	6	−	−	+	+	+	−	−	±	Miliary
N. Y.	7	+	+	+	−	+	−	−	+	Miliary
N. Y.	6	+	+	−	−	+	−	−	−	Other calcifications
N. Y.	11	+	+	+	+	+	+	−	+	Miliary
N. C.	3	−	−	+	−	+	−	−	+	Negative
N. Y.	7	+	+	..	+	+	−	..	−	? Miliary

* Skin tests: T = tuberculin; H = histoplasmin; B = blastomycin; C = coccidioidin.

symptoms presumably due to the illness. All twenty-five men tested with histoplasmin gave a positive reaction to the skin test. Positive reactions to skin tests with tuberculin, blastomycin and coccidioidin were considerably less frequent. Serologic tests were completed on twenty-four of the twenty-six men in this group, and seven of the serums were positive in one of the three tests employed. In addition, serums from nine men were doubtfully positive. Only eight were completely negative.

The most striking findings were revealed by roentgenograms of the chest. As already noted, during the acute illness a disseminated type of pneumonitis occurred which later tended to become nodular in character and faded slowly during the period of observation. Later examination showed that calcification had developed in the lungs and in most cases it was of a miliary type involving all lobes. (Figs. 1 to 8.) In nineteen of the twenty-six men in Group A miliary or multiple calcifications developed. (Table 1.) Similar types of calcification appeared to be developing in three additional cases. Two other cases revealed calcification not of the disseminated type. One case showed healed pleurisy and in only one was the roentgenogram of the chest normal.

It is notable (Table 1) that the major place of residence prior and subsequent to Army service was not in the endemic area of histoplasmosis in any of the cases. Although the data are not

TABLE II

SUMMARY OF CAMP GRUBER FOLLOW-UP STUDIES

Hospitalization, Camp Gruber		Veterans' Compensation	Status at Time of Follow-up						
Duration (months)	Symptoms at Discharge		Symptoms Present	Skin Tests*				Serology	Pulmonary Infiltration
				T	H	B	C		
Group A: Cases Definitely Related to Storm Cellar, March 1944 (Total, Twenty-six Men)									
1–3 mo., 2	18/25	13/23	15/24	9/25	25/25	4/25	2/24	7 positive	Miliary 18 ? Miliary 3
3–5 mo., 4	.....	.....	.....	....	.....	....	....	9	Multiple calcifications 1
5–7 mo., 9	.....	.....	.....	....	.....	....	....	doubtful	Other calcifications 2
7–9 mo., 4	.....	.....	.....	....	.....	....	....	....	Pleurisy 1
9–11 mo., 7	.....	.....	.....	....	.....	....	....	8 negative	Negative 1
Group B: Patients with Characteristic X-ray Picture in 1943 (Total, Three Men)									
3 wk., 1 6 mo., 2	0/3	0/3	1/3	2/3	3/3	1/3	0/3	0/3	Miliary 3
Group C: Control Subjects from Whom Blood Specimens Were Secured in May 1944†									
1 wk., 2	0/8	0/8	0/8	4/8	4/8	0/8	1/8	0/8	Other calcifications 1 Negative 7

* See footnote, Table I. The numerator of the above fractions indicates the number of men having positive reaction or symptoms, and the like; the denominator is the number tested or on whom information is available.

† These men (total, eight) were members of the same organization but remained well.

available, it is reasonable to assume that histoplasmin skin tests gave negative results in these persons prior to the illness. Thirteen of the men resided in the northeastern states and eight in the southeastern states. The remainder were scattered, with one from Hawaii.

Comparative data (Table II) for Groups A, B and C reveal that the disease in the three men in whom the illness occurred in 1943 subsequently followed a course similar to that of the men who were hospitalized during the outbreak in 1944 (Group A). All three men (Group B) have disseminated pulmonary calcification that is demonstrable roentgenographically, all gave a positive reaction to histoplasmin and one still has pulmonary symptoms. Specific antibodies for H. capsulatum have not been detected in the serums, none has been discharged from the Army as a result of the illness at Camp Gruber and none is receiving veteran's compensation.

The results of the follow-up studies in Group C, the eight men who remained well although they were members of the same organization as the men involved in the epidemic, were in sharp contrast to the results of follow-up studies in Groups A and B. Diffuse pulmonary calcification was not demonstrable, only half of the men gave positive reactions to histoplasmin, specific antibodies for H. capsulatum were not demonstrable in the serums and all were free of significant pulmonary symptoms at the follow-up examination.

COMMENTS

The accumulated evidence furnished both by previously published data and by the results of the comprehensive follow-up studies reported here clearly indicates that the outbreak in 1944 at Camp Gruber was caused by H. capsulatum. The evidence may be summarized as follows: (1) the presence of a positive skin test

reaction to histoplasmin in all men who were known to have had the characteristic pulmonary lesions both in 1943 and in 1944, (2) the presence of specific antibody for H. capsulatum demonstrable in the serums obtained during the convalescent phase in 1944, (3) the presence of similar antibody in serums collected during postconvalescence in 1950 and 1951 but in reduced titer when compared with the specimens collected in 1944, (4) the development of miliary calcification demonstrable roentgenographically in the chest films of the majority of the men in whom diffuse pulmonary infiltration was revealed both in 1943 and in the outbreak of 1944 and (5) the isolation of H. capsulatum from the abandoned storm cellar which epidemiologically was the common source of exposure. Although the evidence is convincing that H. capsulatum was the cause of the epidemic, the organism was not isolated from any of the patients. In retrospect, it seems likely that the organism was present in some of the specimens collected in 1944. The cultures were observed for an insufficient period, however, and subcultures of the organs of the mice injected with sputums were not made since gross disease was not noted at autopsy of these animals.

The airborne character of the common source of exposure in the storm cellar seems reasonable. Small fires were built of bark and chips chopped from the tree supports of the roof in an underground cellar, the only opening of which was closed with a blanket. The closed chamber and the hot air currents created ideal conditions for the airborne dissemination of spores which could have been inhaled by the occupants. The organism was isolated from the site at which the fires were built, as well as from several other sites in the cellar.

The results of the present study re-emphasize the severity of the disease which in these instances resulted in prolonged hospitalization of the men involved, in disability discharge from the Army for three-fourths of the men and in persistence in many of pulmonary symptoms some six to seven years after the epidemic.

The similarity of the outbreak recorded here to several other outbreaks resulting from common exposure and producing similar illnesses with pulmonary infiltration is striking.[12,13] It is possible that certain of these epidemics recorded in the literature may also have been due to H. capsulatum.

SUMMARY

An epidemic of disseminated pulmonary disease which occurred at Camp Gruber, Oklahoma, in 1944, following common exposure in an abandoned storm cellar, is reviewed. On the basis of the results of the comprehensive follow-up study reported here and certain other data which have accumulated in the literature since the occurrence of the epidemic, it is concluded that the outbreak was due to H. capsulatum. This is the first epidemic finally proved to have been caused by histoplasmosis.

Acknowledgment: The authors wish to thank Dr. Charles E. Smith, University of California School of Public Health, Berkeley, who was the first to suggest H. capsulatum as the possible cause of this epidemic because of the suggestive serologic results obtained by him in 1944 from serums from the patients.

This study would have been impossible without the cooperation of the Veterans Administration and the National Research Council through the use of their locator files, and of the Regional Medical Directors of the Public Health Service and the State Health Officers. Through these channels the patients and the local health officers and private physicians were reached and the follow-up reported herein was performed by one of these groups. The wholehearted cooperation of the patients, private physicians and local health officers is gratefully acknowledged.

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Ox Cell Hemolysins in Infectious Mononucleosis and in Other Diseases*

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This study was undertaken to evaluate the diagnostic significance of hemolysin for ox cells which occurs in the serum of patients with infectious mononucleosis. In 1935 Bailey and Raffel[1] described hemolysin for ox cells that appeared in the serum of three patients with infectious mononucleosis. Mason[5] in 1951 concluded that the ox cell hemolysin test was as sensitive and specific as other serologic tests for the diagnosis of infectious mononucleosis. In 1952 a careful study was made of this hemolysin when Leyton[7] examined 987 serums of an undesignated number of patients. He concluded that an ox cell hemolysin test is more valuable in the diagnosis of infectious mononucleosis than is the heterophil antibody test. The results of the present study support Leyton's conclusions.

The titer of the ox cell hemolysin in infectious mononucleosis generally becomes of diagnostic value during the first week of illness and usually remains significantly elevated for a longer period than does the titer of the heterophil antibody test. A single random specimen taken during the illness is therefore more likely to show a diagnostic titer with the ox cell hemolysin test than with the heterophil antibody test. The test is simple and may be completed within half an hour after inactivation of the serum. It is a valuable aid in differentiating infectious mononucleosis from diseases with which it may be confused on clinical or laboratory grounds, notably infectious hepatitis, the lymphomas and various respiratory infections.

MATERIALS AND METHODS

Serum specimens were obtained from 351 patients and examined by ox cell hemolysin and heterophil antibody tests. A diagnosis of infectious mononucleosis was considered by the admitting physician for 291 of these patients, most of whom were hospitalized. Ten patients were selected whose conditions would enlarge the list of diseases that might be confused with infectious mononucleosis. The remaining fifty patients were hospitalized random control subjects. Multiple serum samples were obtained in many cases. All cases were considered in the light of the four diagnostic criteria emphasized by Leibowitz.[6] These criteria are: (1) the clinical picture of infectious mononucleosis, (2) a lymphocytosis with over 10 per cent Downey cells in the peripheral blood, (3) a significant heterophil antibody titer including a typical adsorption pattern with guinea pig kidney and beef cell antigens and (4) abnormal liver function tests. Such an approach yields an adequate diagnostic background for evaluation of the specificity and reliability of the ox cell hemolysin test. In this regard specificity refers to the occurrence of false positive reactions and reliability as to the occurrence of false negative reactions.

Ox Cell Hemolysis Test. The serum was inactivated at 56°c. for thirty minutes and serial dilutions of 0.5 ml. were made in 0.85 per cent NaCl containing 0.1 gm. $MgSO_4$ per L. To each tube of the diluted serum were added 0.5 ml. of a 1 in 15 dilution of complement and 0.5 ml. of a 2 per cent suspension of beef cells. The tubes were incubated in a 37°c. water bath for fifteen minutes, centrifuged and compared with a 50 per cent hemolysis standard. The report was based upon the reciprocal of the highest final dilution of the serum which showed 50 per cent hemolysis of the beef cells. Reconstituted lyophilized complement† was found to give more consistent results than fresh complement. Beef cells were collected at weekly intervals in Alsever's solution. Cells more than a week old may not give consistent results in performance.

Heterophil Antibody Test. Modified Stuart's method was used as previously described by Goldman, Fishkin and Peterson,[4] except that the tubes were returned to the 37°c. water bath for thirty minutes following the incubation period in the refrigerator and before the

† Sharp and Dohme, Inc.

* From the Laboratory Service, Veterans Administration Center, Los Angeles, and the Departments of Pathology and Medicine, University of California at Los Angeles. This study was aided in part by a grant from the Blood Bank of San Bernardino-Riverside Counties.

TABLE I

HIGHEST OX CELL HEMOLYSIN TITERS IN 351 PATIENTS CLASSIFIED ACCORDING TO DISEASE*

Diagnosis	Highest Titer						
	480 or Above	240	120	60	30	15	Negative
Infectious mononucleosis	21	1	0	0	0	0	1†
"Probable" infectious mononucleosis	4†	2†	0	0	0	0	0
"Questionable" infectious mononucleosis	2†	0	1†	0	0	0	0
Infectious hepatitis	0	1	2	2	2	3	19
Chronic myeloid leukemia	0	0	0	0	0	0	4
Chronic lymphatic leukemia	0	0	0	0	0	0	1
Acute monocytic leukemia	0	0	0	0	0	0	1
Lymphosarcoma	0	0	0	0	0	0	3
Hodgkin's disease	0	0	0	0	0	0	5
Upper respiratory infection	0	0	1	0	0	1	13
Pneumonia	0	0	0	0	0	0	5
Miscellaneous	1†	1	7	2	12	15	218
Totals	28	5	11	4	14	19	270

* A titer of 480 or above is indicative of infectious mononucleosis; low or negative titers are found in infectious hepatitis, lymphoma, respiratory infections and miscellaneous conditions.

† Complete data on these cases are given in Table III.

final reading. The test was modified in this manner to avoid reactions due to cold hemagglutinins for sheep cells.

Guinea Pig Kidney and Beef Cell Antigen Adsorption Studies. Serum was adsorbed with guinea pig kidney and boiled beef cell antigen as described by Davidsohn.[3] The adsorbed serum specimens were then examined at the same time as the unadsorbed specimens in the manner already described.

Liver Function Tests. Thymol turbidity and cephalin flocculation tests were performed according to standard technic.[5] The cephalin flocculation results recorded in this paper were read at twenty-four hours.

RESULTS

The highest ox cell hemolysin titer for each of the 351 patients examined is indicated in Table I. A comparison of the ox cell hemolysin and heterophil antibody titers of the twenty-three patients in whom infectious mononucleosis was definitely established is given in Table II. These patients fulfilled at least three and frequently all four of the diagnostic criteria of Leibowitz.[5] All patients presented a clinical picture typical of infectious mononucleosis. Nineteen showed a heterophil antibody adsorption pattern characteristic of infectious mononucleosis. Significant hematologic and blood chemistry findings for the twenty-three patients were as follows: white blood count over 10,000 per cu. mm. in sixteen patients, less than 10,000 per cu. mm. in seven; lymphocytes over 40 per cent in all cases and over 60 per cent in twenty; Downey cells over 10 per cent in thirteen subjects, present but percentage not indicated in six, present but less than 10 per cent in two and not found in two; thymol turbidity test over five units in twenty persons, not performed in three; cephalin flocculation test 2 plus to 4 plus in twenty-four hours in seventeen patients, negative reactions in three and not done in three.

Fifteen cases requiring individual consideration are described in some detail in Table III. These include all cases from Table I which were classified as "probable" or as "questionable" infectious mononucleosis. Such patients presented features suggesting infectious mononucleosis but fulfilled less than three of the diagnostic criteria used in this study. Five cases of definite infectious mononucleosis with low or negative heterophil antibody titers and one considered a false positive elevation of the ox cell hemolysin titer are also cited in detail in Table III.

Serial ox cell hemolysin titers and heterophil antibody titers on eight patients in whom infectious mononucleosis was definitely established are indicated in Figure 1. Results of thymol turbidity and cephalin flocculation studies are also presented there.

The adsorption pattern with the guinea pig kidney antigen and the boiled beef cell antigen

for the ox cell hemolysin test was generally similar to that observed with the heterophil antibody test. No definite relation was noted between the height of the ox cell hemolysin titer and the severity of the clinical disease.

COMMENTS

As the ox cell hemolysin test is performed in this laboratory, a titer of 480 or above constitutes strong presumptive evidence for the diagnosis of infectious mononucleosis. Leyton[7] considered 60 or above a diagnostic titer. The difference may be due to variations in technic.

We have employed the term "ox cell hemolysin" in place of "beef cell hemolysin" in this report in deference to the original investigators. Ox cells and beef cells are essentially identical.

The ox cell hemolysin titer in most cases of infectious mononucleosis attains diagnostic value during the first week of clinical illness. However, in Case 1 of Table III a significant titer was not reached until the twenty-third day of illness and in Case 8 among the "probable" cases a significant titer was not recorded until the twenty-eighth day. The ox cell titer remains significantly elevated beyond the sixth week following onset in the majority of cases of infectious mononucleosis. Case 3 among the "definite" cases and Cases 6 and 7 among the "probable" ones of Table III are apparent exceptions to this statement. Despite occasional exceptions, a prompt rise and slow fall in titer of the ox cell hemolysin is the general rule in this disease. Titration of ox cell hemolysin would seem, on the basis of this small series, to be more reliable than titration of heterophil antibody in the diagnosis of infectious mononucleosis when specimens of serum are examined at random during the course of the disease. Figure 1 illustrates this point. Here we see that, of forty random determinations of ox cell hemolysin and heterophil antibody performed simultaneously on serums from eight patients in whom infectious mononucleosis had been definitely established, diagnostic titers were recorded thirty-two times for ox cell hemolysin and only twenty-three times for heterophil antibody. Table II shows that five of twenty-three cases of infectious mononucleosis which had been definitely established failed to demonstrate a heterophil antibody titer of 80 or above in random serum specimens, whereas only two failed to demonstrate an ox cell titer of 480 or above. The low or negative heterophil antibody titers of these patients may have resulted from obtaining the specimens after the titer was declining. One patient who definitely had infectious mononucleosis (Case 4, Table III) gave a negative reaction to the ox cell hemolysin test.

The ox cell hemolysin titration seems to present a high degree of reliability as an aid in

TABLE II

COMPARISON OF HIGHEST OX CELL HEMOLYSIN TITER WITH HIGHEST HETEROPHIL ANTIBODY TITER FOR TWENTY-THREE CASES OF DEFINITE INFECTIOUS MONONUCLEOSIS *

No. Patients	No. Days from Onset of Illness	Ox Cell Hemolysin Titer	Heterophil Antibody Titer †
1	22	122,880	320:160:20
3	5	61,440	640:640:160
	9	61,440	320:80:negative
	7	61,440	160:80:negative
1	30	30,720	640:320:80
1	31	15,360	1280:320:negative
1	21	7,680	160:160:negative
2	15	3,840	320:160:negative
	8	3,840	80:80:negative
8	18	1,920	640:640:640 ‡
	26	1,920	640:640:160
	14	1,920	640:640:80
	34	1,920	640:640:negative
	5	1,920	640:160:negative
	24	1,920	160:320:negative
	7	1,920	160:not done
	19	1,920	40:40:negative §
2	60	960	20:not done §
	25	960	negative §
2	12	480	640:640:negative
	25	480	640:320:negative
1	24	240	40:negative: negative §
1	..	negative	40:not done §

* In thirteen of these cases only a single serum specimen was available.

† Titers as follows: unadsorbed serum; after adsorption with guinea pig kidney antigen; after adsorption with beef cell antigen.

‡ Patient was not available for recheck. Lack of adsorption by the beef cell antigen is suspected of being a technical error.

§ These five cases are cited in greater detail in Table III as Cases 1 to 5 inclusive.

TABLE III

CLINICAL AND LABORATORY DATA ON FIVE CASES OF INFECTIOUS MONONUCLEOSIS WITH LOW OR NEGATIVE HETEROPHIL ANTIBODY TITERS; SIX CASES OF "PROBABLE" INFECTIOUS MONONUCLEOSIS; THREE CASES OF "QUESTIONABLE" INFECTIOUS MONONUCLEOSIS; AND ONE INSTANCE OF PROBABLE FALSE POSITIVE ELEVATION OF OX CELL HEMOLYSIN TITER

Case	Clinical Picture	Illness (days)	Hematologic Data			Serologic Data		Liver Function	
			White Cell Count	Lymphocytes (%)	Downey Cells (%)	Heterophile Titer	Ox Cell Hemolysin Titer	Thymol Turbidity	Cephalin Floc. (24 hr.)
Definite Infectious Mononucleosis with Low or Negative Heterophil Antibody Titers									
1	Sore throat, fever, lymphadenopathy, palpable liver and spleen	8	15,200	70					
		11	11,900	80	over 10	20		8.6	2+
		15	27,200	82		negative	120	8.6	4+
		23	8,860	60		negative	480		
		31	7,950	47	few	negative	480		
		47	5,240	46		negative	480		
		60	5,600	41		negative	960	9.0	
2	Sore throat, malaise, headache, fever, lymphadenopathy, palpable liver and spleen	21	15,600	78	over 10			11.0	3+
		25	11,300	71		negative	960	11.0	2+
		28	5,500	72					
		39	5,200	60		negative		8.1	negative
		55				negative	960		
		62	5,200					4.0	negative
3	Cervical lymphadenopathy	1	4,500	34	few				
		2		58	24				
		11	11,000	75					
		24	11,000	75		40:negative:negative	240	8.1	3+
		73				negative	240	4.0	3+
4	Fever, cough, malaise, slight axillary lymphadenopathy, enlarged tender spleen	8	8,900	39	few		negative		
		10	6,200	45	few				
		12	8,300	66	over 10	negative		6.6	negative
		15	9,200	73		40:not done:not done			
		19					negative	6.6	negative
		26	6,000	60		negative			
		33				negative			
5	Several episodes of cervical lymphadenopathy	18	15,700	81	over 10	40:40:negative	1920	12.0	4+
		41				20	1920	7.7	3+
Probable Infectious Mononucleosis									
6	Sore throat, headache, lymphadenopathy, fever, palpable tender liver, pain on movement of eyes	26	13,400	65	present,				
		27	9,100	57	% not	negative	240		
		35	6,800	57	recorded	negative	240		
7	Sore throat, fever for five days, cervical adenopathy; clinical of Vincent's infection not confirmed bacteriologically; abnormal EKG; biopsy of Hodgkin's disease, 1951	4	12,500	74	present,				
		6	18,500	63	% not				
		19			recorded	20			
		26				80	240		
8	Sore throat, cervical adenopathy, headache, five days of fever, malaise, photophobia	20	20,200	84	75	20:20:negative	240	3.7	negative
		28				20:40:negative	3840		
9	Sore throat and lymphadenopathy	5		76	present,				
		19		72	% not recorded	negative	480		
10	Sore throat, fever, tender palpable spleen	8	6,700	71	present, % not recorded	10	1920		
11	Sore throat, malaise, fever and lymphadenopathy	3				negative	30		
		10	7,500	78	78	10	1920		
Questionable Infectious Mononucleosis									
12	"Fever of undetermined origin." Had received tetanus booster ten days prior to onset, history of previous similar reaction after "shots" in army	3	10,200	15	none	80	960		
		5				320:160:20			
		9				80:80:negative	30		

TABLE III (*Continued*)

Case	Clinical Picture	Illness (days)	Hematologic Data			Serologic Data		Liver Function	
			White Cell Count	Lymphocytes (%)	Downey Cells (%)	Heterophile Titer	Ox Cell Hemolysin Titer	Thymol Turbidity	Cephalin Floc. (24 hr.)
					Questionable Infectious Mononucleosis				
13	Acute meningitis of unknown etiology, with coma and convulsions. Spinal fluid: increased lymphocytes, elevated globulin and protein. Treated with antibiotics and steroids. Recovered	4 12 17 38 44	23,700 16,000 16,200 9,600	11 21 27 30	none	 160 160:320:negative	 480		
14	Fever for four days; latent syphilis with positive TPI test	4 10 23 31 33 37	10,400 12,200 12,450	14 19 17	 none	 160:160:not done 320:180:not done 320:40:10	 120 120 120	 11.5	 negative
					Instance of Probable False Positive Elevation of Ox Cell Hemolysin Titer				
15	Parrot bite on arm one week prior to onset; onset with three days of chills, perspiration, vertigo, weakness and numbness of legs, nuchal rigidity	6 11	7,200	34	none	 20	 960		

the diagnosis of infectious mononucleosis, since the occurrence of false negative reactions is infrequent. The specificity of the test, including the possible occurrence of false positive reactions, requires separate consideration.

Table I gives the highest ox cell hemolysin titers recorded in 351 patients classified according to disease. Of these, twenty-three had "definite" infectious mononucleosis, six "probable" and three "questionable" infectious mononucleosis. Opinion regarding the specificity of the ox cell hemolysin titration would be influenced by evaluation of these "probable" and "questionable" cases. As the data are fully given in Table III, the reader may draw his own conclusions with regard to these individual cases.

Among the 351 patients of Table I were twenty-nine cases of infectious hepatitis, fourteen of lymphoma and eighteen of respiratory infection. All of these gave negative or non-diagnostic ox cell hemolysin titers. A slight elevation of the titer is sometimes seen in infectious hepatitis.

One patient of the 351 gave what the authors classified as a false positive reaction. Details of this case are given in Table III (Case 3). This patient fulfilled at most only one of Leibowitz's criteria (clinical history) but was not followed for a sufficient period to rule out the development of further diagnostic signs. The patient was not investigated for psittacosis despite the history of a parrot bite. However, serums from six patients giving positive complement fixation tests for psittacosis* yielded negative reactions with the ox cell hemolysin test. Beer[2] has demonstrated that recent injections of horse serum may cause an elevation of both ox cell hemolysins and sheep cell agglutinins. This patient had no history of horse serum injections.

In Case 12 among the "questionable" group of Table III it was believed that a recent tetanus "booster" shot might have been responsible for the elevated serologic tests. Therefore, eight volunteers received tetanus "booster" shots, and both heterophil antibody and ox cell hemolysin tests were performed on serums from these persons three times a week for two weeks. No elevation in titer was found with either test.

It may be noted from Figure 1 that the curve of the ox cell hemolysin titer in some cases is similar to that of the heterophil antibody titer. The adsorption patterns of the antibodies with guinea pig kidney and beef cell antigens are also similar. However, Leyton[7] has demonstrated by adsorption procedures that the antibodies responsible for these reactions are not identical.

* Obtained from the George Williams Hooper Foundation, San Francisco, California.

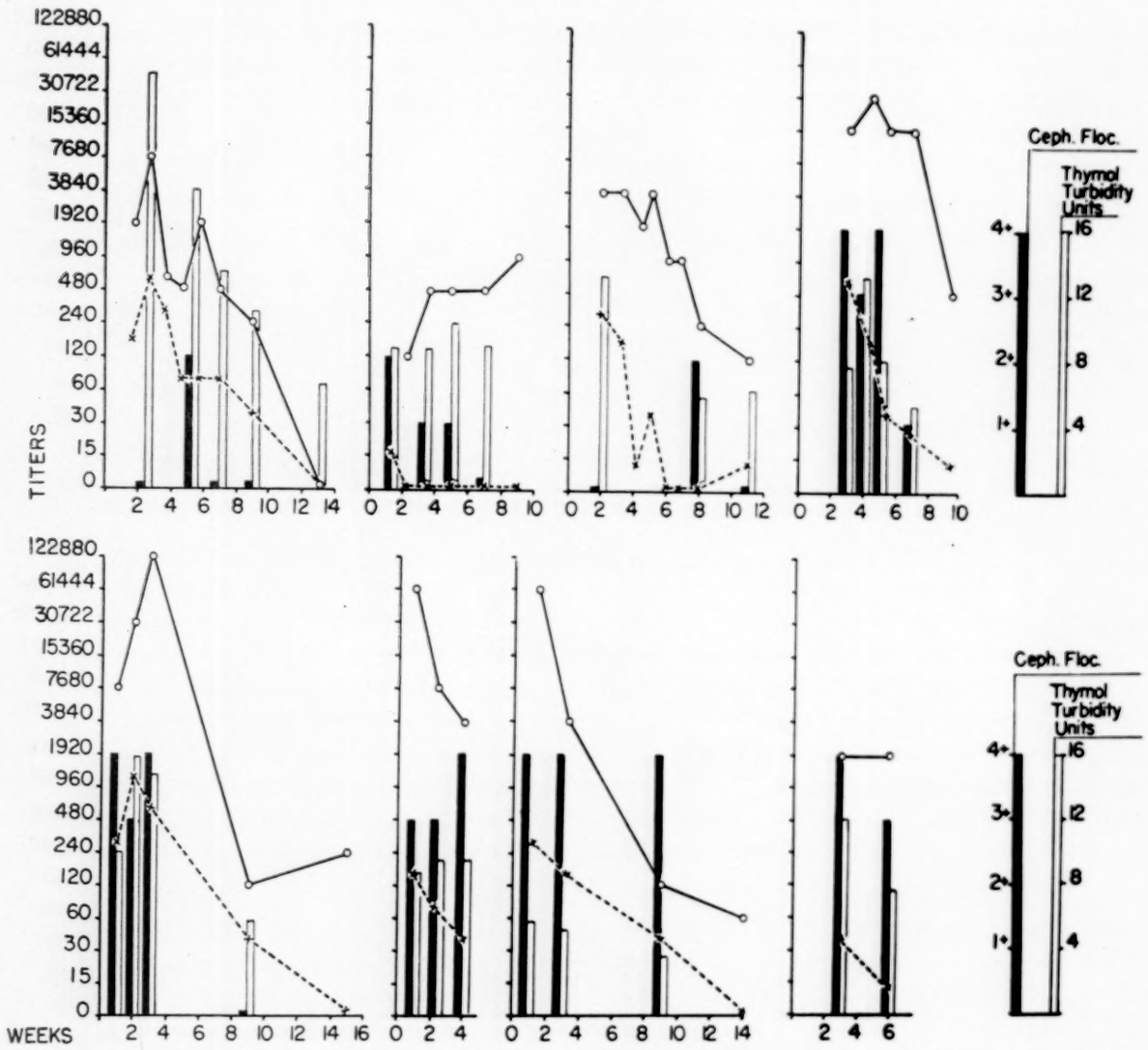

FIG. 1. Ox cell hemolysin titers, heterophil antibody titers and results of liver function tests of eight patients with infectious mononucleosis. The solid line represents ox cell hemolysin titer, the broken line heterophil antibody titer.

SUMMARY

The ox cell hemolysin test in the routine diagnosis of infectious mononucleosis is evaluated. Three hundred fifty-one patients were studied. Among these, twenty-three had "definite" infectious mononucleosis, six were classified as "probable" and three as "questionable" infectious mononucleosis.

The diagnostic criteria used in this study are presented in detail. Twenty-nine patients with infectious hepatitis, eighteen with respiratory infection, eight with lymphoma and six with leukemia all of whom gave non-significant titers, are included in this study. Serial titers of ox cell hemolysins and heterophil antibodies are tabulated for a four to sixteen week period following onset of symptoms.

For specimens taken at random during the disease, the ox cell hemolysin test is more reliable than the heterophil antibody test and probably of equal specificity in the diagnosis of infectious mononucleosis. In problematic cases, the performance of both the ox cell hemolysin and the heterophil antibody tests may give more diagnostic information than either test alone.

Conclusive results cannot be drawn from the small series of cases herein presented but our findings, in agreement with those of Leyton,[7] suggest that the test is worthy of further investigation.

Acknowledgment: We are indebted to Dr. Gertrude T. Huberty, Student Health Service, University of California School of Medicine, for supplying a number of the serum specimens used in this study.

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A Clinical Study of One Hundred Cases of Severe Aortic Insufficiency*

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SINCE the first cases of aortic insufficiency were described by William Cowper in 1706[1] the medical treatment of patients with aortic insufficiency of severe degree has been unsatisfactory. Aortic insufficiency may be present, to be sure, for many years without producing signs or symptoms of congestive failure,[2–10] but after symptoms develop the course may be rapidly downhill.[11–17] Prior to a few years ago, the majority of writers postulated that patients with aortic insufficiency succumbed rather rapidly after the development of failure, but with better diagnosis and the inclusion of cases of milder degree the apparent survival time has increased to a mean of five to six years or even longer.[6,10,18,19]

Longevity statistics vary in the literature and deal almost exclusively with syphilitic aortic insufficiency. In general, once failure develops the prognosis is better in the rheumatic group than in the syphilitic group. Failure in rheumatic cases is often due to recurrent or continued rheumatic activity, and remissions and exacerbations may occur over a period of several years whereas patients in the syphilitic group are more prone to continuous progressive failure.[3,5,17,20] Signs of poor prognosis are severe precordial pain, severe congestive failure, cardiac enlargement, low diastolic pressure, prolonged circulation times, increased P-R interval, T wave inversion in lead II and active endocarditis.[6,8,17,21]

Now that surgical correction is being performed for severe degrees of aortic insufficiency, it has become particularly important that more be known about the natural clinical course of this valvular lesion. This is necessary so that patients may be more wisely selected for cardiac surgery and more objectively evaluated postoperatively in terms of the usual natural course of the disease. Of particular importance would be the course and prognosis of the disease once congestive heart failure and/or angina pectoris develop.

At Georgetown University Medical Center in the past several years we have had the unusual opportunity to study intensively more than 100 patients with severe aortic insufficiency.[22,23] Most of the patients have been referred to this institution for cardiac evaluation in respect to insertion of the Hufnagel aortic plastic valve. Many interesting and unusual clinical features have become evident and some of these will be discussed. Particular emphasis will be given the natural history of the disease.

MATERIAL AND METHODS

It should be emphasized that only patients with severe aortic insufficiency are included in this study. In case selection we have used the following criteria to determine the presence of advanced aortic insufficiency: (1) loud blowing aortic diastolic murmur; (2) wide pulse pressure; (3) low diastolic pressure; (4) fluoroscopic evidence of free aortic insufficiency as indicated by a "rocking" motion of the heart, and marked systolic expansion of the aorta referred to as systolic aortic "jump"; (5) peripheral signs of aortic insufficiency and (6) carotid, subclavian or aortic pulse tracings consistent with free aortic regurgitation. If a patient fulfilled these criteria, and if complete clinical records were available, he was included in this study. All patients were evaluated personally by one of the authors.

The routine evaluation consisted of a complete history and physical examination and in many instances a detailed check sheet which incorporated special features which were of particular interest. A blood count, urinalysis, chest x-ray, cardiac fluoroscopy and electrocardiogram were performed in every case.

We have found previous classifications of cardiac

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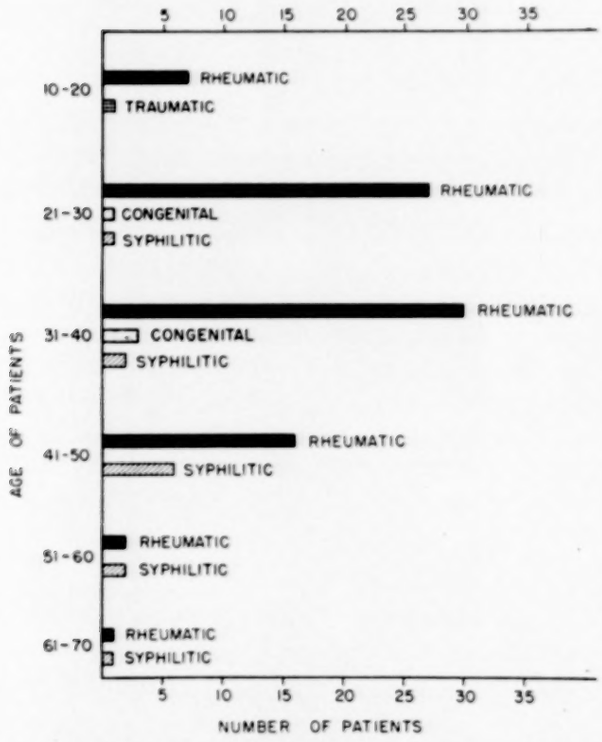

FIG. 1. Etiology and age distribution of 100 cases of severe aortic insufficiency. The majority of cases were rheumatic and occurred between the ages of twenty-one to fifty years.

disease unsuitable for grouping patients with free aortic insufficiency. The following classification, into four categories, is based on symptomatology, cardiac size by x-ray evaluation, and the electrocardiogram: Group A—signs of free aortic insufficiency with absence of any signs or symptoms of congestive heart failure or angina pectoris; electrocardiograms and chest x-rays normal. Group B—asymptomatic or mild symptomatology (dyspnea with only extreme exertion); no angina pectoris; electrocardiogram indicating left ventricular hypertrophy and/or x-ray evidence of slight left ventricular enlargement. Group C—dyspnea and/or angina pectoris with every day activity; x-ray evidence of moderate or marked left ventricular enlargement and electrocardiographic evidence of left ventricular hypertrophy. Group D—disabling congestive heart failure and/or angina pectoris present at rest; x-ray evidence of advanced left ventricular enlargement and left ventricular hypertrophy by the electrocardiogram.

RESULTS

Figure 1 incorporates the etiology and age of 100 patients with severe aortic insufficiency. Rheumatic fever occurred most commonly. Eighty-three patients were rheumatic, twelve syphilitic, four congenital, one traumatic.

Age and Sex. Men predominated in a ratio of 3 to 1. Of the 100 patients twenty-five were women and seventy-five men. Eighty-six per cent were from twenty-one to fifty years of age. The average age of the women was thirty-three, of the men thirty-five. (Fig. 2.)

Rheumatic cases: The majority of the rheumatic patients were from twenty-one to forty years of age. There were sixty men (average age thirty-four years) and twenty-three women (average age thirty-three years). Although men predominated almost 3 to 1 in the group with pure aortic insufficiency, in the eight patients with associated mitral stenosis women predominated 3 to 1 (six women and two men). The average age of the six women with associated mitral stenosis was thirty-six years and of the two men with associated mitral stenosis forty-two years.

Syphilitic cases: The average age in twelve patients was forty-six years (age forty-seven in ten men and age forty-two in the two women).

Congenital cases: All were men and the average age was thirty-two.

Traumatic cases: An eighteen year old boy was the only patient in this category.

Functional Classification. Of the 100 patients,

one was in group A, sixteen in group B, fifty-five in group C, twenty-eight in group D.

Rheumatic cases: Of the eighty-three patients, one was in group A, fourteen in group B, forty-seven in group C and twenty-one in group D. (Table I.) As might be postulated the severity of the heart disease increased with age. The average of the patients in group B was twenty-eight years, in group C thirty-four and in group D thirty-eight. The degree of cardiac disability was also directly proportional to the duration of cardiac symptoms. The sixty-one patients in groups B and C were symptomatic for an average of 5.6 years while the twenty-one patients in group D had symptoms for an average of 8.9 years. Of the thirty-two patients who had symptoms of both angina pectoris and congestive heart failure thirteen (41 per cent) were in group D. Forty-two patients had either congestive failure or angina alone; of these patients only eight (19 per cent) were in group D. Thus it is evident that patients with both angina and congestive failure had more serious heart disease than those with angina or congestive failure alone.

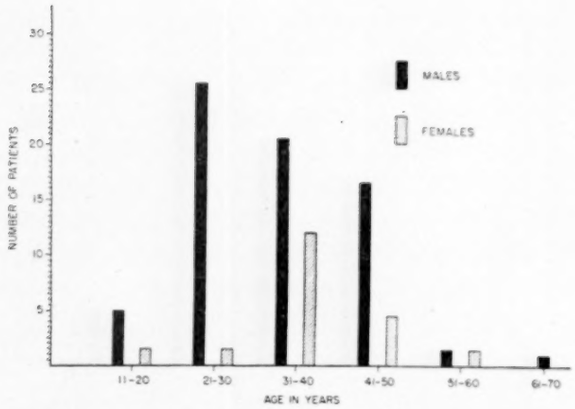

FIG. 2. Age and sex distribution of 100 cases of severe aortic insufficiency. Seventy-five per cent of the patients were men. Eighty-six per cent occurred between the ages of twenty-one to fifty.

Syphilitic cases: Table II correlates the functional grouping with the duration and nature of symptomatology. Of the twelve patients, one was in group B, seven in group C and four in group D. The average age of the patients in group B was forty-six years, in group C forty-three and in group D fifty-one. Of the six patients with both angina and failure one was in group B, four in group C and one in group D. Of the five cases with failure only two were in group C and three in group D.

Congenital cases: Of the four patients, one was in group C and three in group D.

Traumatic cases: This patient was in group D.

TABLE I

RHEUMATIC AORTIC INSUFFICIENCY (83 CASES)

Correlation of Average Duration of Congestive Failure and Angina Pectoris with Functional Group Classification

Symptoms	No. of Cases	Average Time from Onset of Symptoms (yr.)	Functional Group			
			A	B	C	D
Congestive failure alone	36	5.2	0	4	25	7
Angina alone	6	4.0	0	0	5	1
Angina and congestive failure	32	7.7	0	2	7	13
Angina followed by failure	8	6.9	0	0	3	5
Angina preceded by failure	10	12.4	0	0	5	5
Onset of angina and congestive failure simultaneously	14	4.9	0	2	9	3
Asymptomatic	9	6.4	1	8	0	0
Total	83	6.4	1	14	47	21

Natural Course of the Disease. Rheumatic cases: Figure 3 summarizes the natural course of our cases. A definite history of rheumatic fever characterized by migratory polyarthritis, fever and the like was obtainable in over 80 per cent of the cases. The average age of occurrence of the initial episode of rheumatic fever could be ascertained in seventy-eight of the eighty-three patients and was found to be thirteen years.

The average time interval from the first episode of acute rheumatic fever to the development of hemodynamically significant aortic insufficiency was seven years, as calculated from data available in fifty-nine cases. Occasionally, free aortic insufficiency followed the episode of acute rheumatic fever by several months, but generally several years elapsed before significant aortic insufficiency developed. In some cases past detailed records containing notations of murmurs and blood pressures specifically indicated when "free" aortic insufficiency was present. In other cases we have deduced the onset of hemodynamically significant aortic insufficiency from associated symptoms such as pounding or throbbing in the head or neck due to increased pulsation of the carotic arteries. In many cases a blowing aortic diastolic murmur was present from the initial episode of acute rheumatic fever, but we do not consider this to be "significant" aortic insufficiency unless the previously mentioned peripheral signs of free aortic

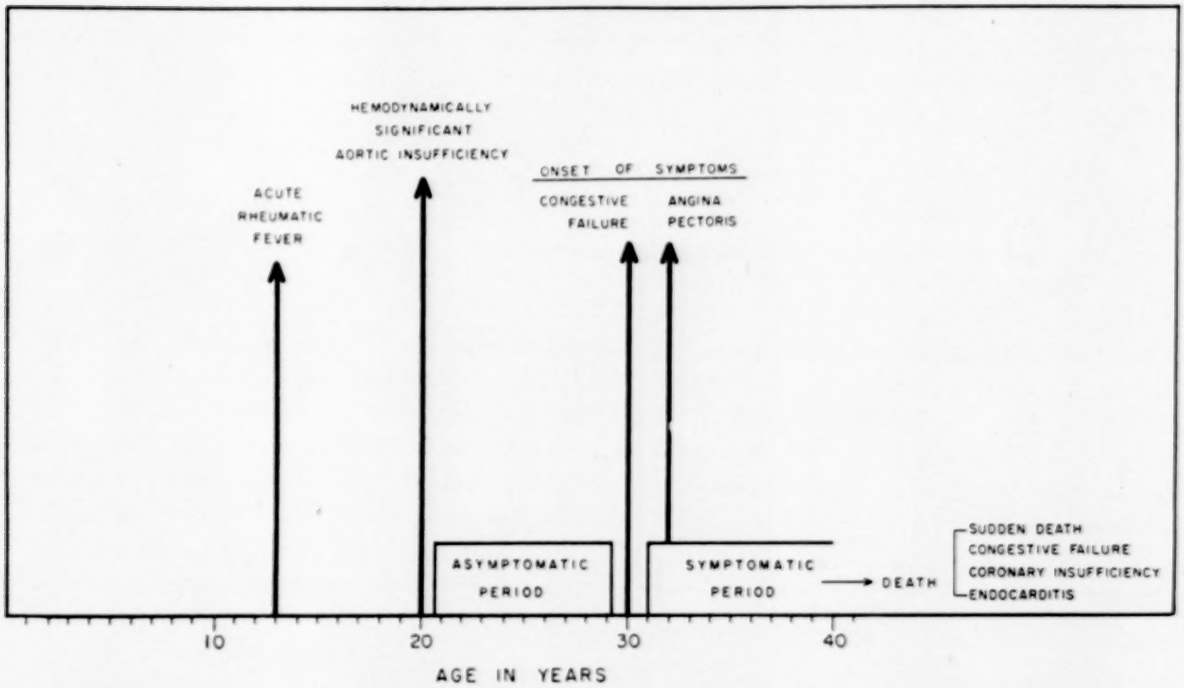

FIG. 3. Clinical profile of eighty-three cases of rheumatic aortic insufficiency. The "average" patient had acute rheumatic fever at age thirteen, hemodynamically significant aortic insufficiency at age twenty. The "asymptomatic" period lasted approximately ten years, with symptoms occurring at about age thirty.

insufficiency or blood pressure recordings indicating a low diastolic pressure is also present. In sixty patients the interval from the onset of free aortic insufficiency to the onset of symptoms was determined. This "asymptomatic" period was found to average 10.3 years. To summarize, the average patient experienced the first episode of rheumatic fever at age thirteen, developed hemodynamically significant aortic insufficiency at age twenty and noticed symptoms of heart disease such as angina pectoris or congestive failure at approximately age thirty.

The final phase from the onset of symptoms to the time of this evaluation is referred to as the "symptomatic" period. The rheumatic patients with severe aortic insufficiency were symptomatic approximately 6.4 years; usually these symptoms were slowly progressive in nature. Many of these patients had superimposed recurrent acute episodes of cardiac decompensation related to low grade rheumatic activity which intermittently subsided and exacerbated. In the seventy-four symptomatic cases the initial complaint was congestive failure in forty-six, angina pectoris in fourteen and a combination of both in fourteen. Thirty-six patients had congestive heart failure with no angina pectoris, six had angina pectoris and no associated congestive failure, thirty-two had both angina pectoris and congestive failure, and nine were asymptomatic. (Table I.)

Figure 4 correlates the duration and frequency of congestive failure and angina. Congestive failure was present in sixty-eight instances; it ranged in duration from two months to thirty years, being present for an average of 6.6 years. In eleven persons failure was present for less than one year, in nineteen from one to three years, in twenty-two from three to ten years, and in sixteen for more than ten years.

Classic angina pectoris was present in thirty-eight patients, occurring predominantly at night in ten. Angina was present for an average of 4.6 years, ranging from four months to twelve years. In three patients it was present for less than a year, in eleven for one to three years, in twenty-two from three to ten years and in two for over ten years. Of particular interest is the fact that the average age of those patients with angina pectoris was 33.7 years, approximately the same age as the group without angina.

Six patients had angina but no congestive heart failure for an average of four years. Thirty-six had failure alone (average of 5.2 years) and

thirty-two patients had both congestive failure and angina pectoris (average of 7.7 years). Further subdividing the group with both failure and angina, of the eight patients who had angina and later developed failure, the average duration of symptoms was 4.9 years. In ten who had congestive failure initially and in whom angina subsequently developed, the average duration of symptoms was 12.4 years. (Table I.)

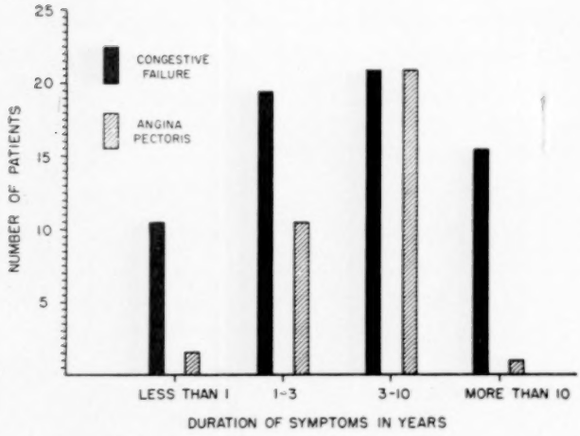

FIG. 4. Duration and frequency of congestive heart failure and angina pectoris in eighty-three patients with severe rheumatic aortic insufficiency. Note that congestive failure was present in twenty-two patients for three to ten years, and for more than ten years in sixteen. Angina was present in twenty-two patients for three to ten years, and for more than ten years in two.

Syphilitic cases: The primary lesion of syphilis was present about age twenty, significant aortic insufficiency developed at about age thirty-six, and symptoms of congestive failure and/or angina pectoris first appeared at about the age of forty-three. Of the twelve patients in the syphilitic group, five had congestive failure alone, six had both congestive failure and angina pectoris, and one patient was asymptomatic. (Table II.) Congestive failure was present in eleven patients for an average duration of 2.5 years, and in six of these angina pectoris was also present for an average of 1.9 years. Of interest, the average age, as in the rheumatic group, was the same whether or not angina pectoris was present.

Congenital cases: Supposedly in these cases the murmur had been present since birth. Two patients had both angina and congestive failure and two had congestive failure alone. The average duration of the failure was three years and angina pectoris had been present four and a half years. In Table III the clinical profiles of the rheumatic, syphilitic and congenital groups are compared.

TABLE II
SYPHILITIC AORTIC INSUFFICIENCY (12 CASES)
Correlation of Average Duration of Congestive Failure and Angina Pectoris with Functional Group Classification

Symptoms	No. of Cases	Average Time from Onset of Symptoms (yr.)	Functional Group			
			A	B	C	D
Congestive failure alone	5	3	...	..	2	3
Angina alone	0					
Angina and congestive failure	6	2	...	1	4	1
Angina followed by failure	1	2	...	..	1	..
Angina preceded by failure	0	..	...	..	..	..
Onset of angina and congestive failure simultaneously	5	2	...	1	3	1
Asymptomatic	1	...			1	..
Total	12	2.4	...	1	7	4

TABLE III
CLINICAL PROFILES OF AORTIC INSUFFICIENCY

	Rheumatic (Age)	Syphilitic (Age)	Congenital (Age)
Etiology	13	20	from birth
Pre-murmur phase*	13–20	20–36	
Onset of murmur	20	36	from birth
Asymptomatic period	20–29	36–43	birth–28
Onset of congestive heart failure or angina pectoris	29	43	28
Symptomatic period (duration in years)	6.4	2.5	4

* Time elapsed between first episode of rheumatic fever or syphilis and the appearance of a significant murmur.

Traumatic case: This patient's symptomatology had been present for two months following a kick in the chest by a horse. He had been hospitalized since that time and was asymptomatic on bedrest.

Specific Symptoms. The relative frequency of specific symptoms, physical findings and laboratory data are tabulated in Table IV.

Rheumatic cases: Figure 5 tabulates the frequency and average duration of specific symptoms. In general, the first symptom was an awareness of increased force of the heart beat, frequently associated with a sensation of pulsation over the precordium and neck. The first symptom of congestive failure was almost always dyspnea related to exertion. Angina pectoris, present in almost half of our cases, usually appeared after the onset of congestive failure.

Dyspnea had been present in sixty-five of the

eighty-three patients for an average of 6.7 years. Paroxysmal nocturnal dyspnea was present in thirty-six patients for an average of 3.7 years and orthopnea in twenty-nine patients for an average of four years. Peripheral edema was noted in only seventeen patients for approximately four years. Palpitation, one of the earliest symptoms observed, was present in forty-nine patients for an average of 6.6 years, and angina in thirty-eight for 4.6 years.

TABLE IV
HISTORY, PHYSICAL FINDINGS, X-RAY INTERPRETATIONS AND ELECTROCARDIOGRAMS

	Rheumatic (83 cases)	Syphilitic (12 cases)	Others (5 cases)
Symptoms:			
Dyspnea on exertion	65 (78%)	11 (92%)	4 (80%)
Orthopnea	29 (35%)	7 (58%)	4 (80%)
Paroxysmal nocturnal dyspnea	36 (43%)	5 (42%)	2 (40%)
Palpitation	49 (59%)	4 (33%)	2 (40%)
Angina	38 (46%)	6 (50%)	2 (40%)
Edema	17 (20%)	5 (42%)	2 (40%)
Physical findings:			
Average blood pressure, 155/37			
Aortic diastolic murmur, 100%			
Aortic systolic murmur, 100%			
Pulmonary rales, 4/46 = 9%			
Hepatomegaly, 25/46 = 54%			
Splenomegaly, 2/46 = 15%			
Edema, 5/46 = 10%			
X-rays (ninety-nine patients analyzed):			
Left ventricular hypertrophy, 97			
Posterior esophageal displacement, 48			
Systolic expansion of the left auricle, 30			
Normal x-ray, 2			
Electrocardiograms (ninety-five patients analyzed):			
Normal sinus rhythm, 88			
AV block (usually first degree), 24			
Left ventricular hypertrophy, 90			
Auricular fibrillation (all with mitral stenosis), 4			
Left bundle branch block (questionable left ventricular hypertrophy), 2			

Syphilitic cases: The symptomatology in the syphilitic group was similar to that observed in the rheumatic but the average duration of symptoms was approximately halved. In other words, the course of the disease was more rapidly downhill in the syphilitic than in the rheumatic group. Dyspnea on exertion was present in eleven patients for an average of 2.5 years, orthopnea in seven for 2.3 years, paroxysmal nocturnal dyspnea in five for 1.5 years and ankle edema in five for approximately 1.4 years. Six patients had angina pectoris for an average of 1.9 years and palpitation was present in three for .8 of a year.

Congenital cases: Dyspnea on exertion was noted in every case and was present for 2.2 years. Orthopnea, palpitation and angina were each present in two cases and paroxysmal nocturnal dyspnea and peripheral edema were present in one.

Physical Findings. Table IV lists the most important physical findings and their frequency. There was no significant difference between the rheumatic, syphilitic and congenital cases. The average blood pressure in ninety-eight patients was 155 systolic and thirty-seven diastolic. In twenty patients the systolic blood pressure was over 160 mm. Hg. In almost every case diastolic sounds could be heard down to zero, but the diastolic pressure was assumed to be that point at which the sounds changed from a sharp to a muffled quality. In every case diastolic and systolic murmurs were heard over the aortic area; and at the apex a systolic murmur, a ventricular gallop and an Austin Flint rumble were present. Hepatomegaly, presumably secondary to congestive failure, was noted in approximately 50 per cent. Splenomegaly was present in 14 per cent.

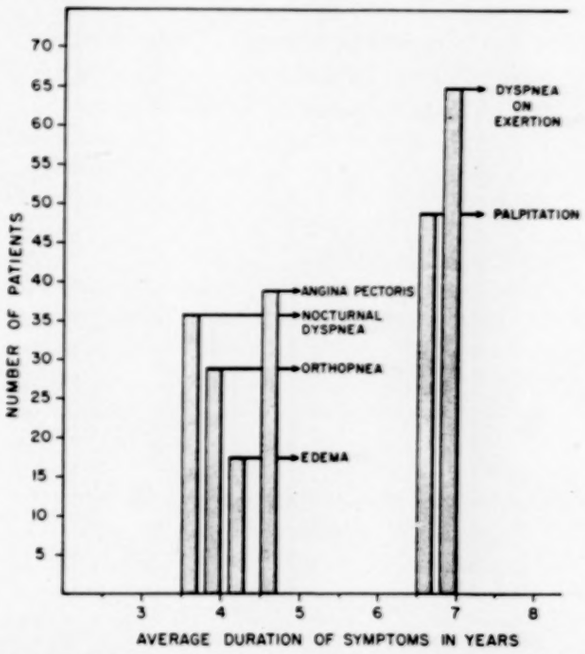

FIG. 5. Duration and frequency of specific symptoms in eighty-three patients with severe rheumatic aortic insufficiency. The first symptoms to appear were dyspnea and palpitation. Angina was present in about 50 per cent of the group.

X-ray Findings. X-rays were available in every case except one, and the cardiothoracic

ratio, which admittedly is only an approximate index of cardiac enlargement, was calculated. The x-ray findings are compiled in Table IV. In ninety-seven of the ninety-nine cases definite cardiac enlargement was present (cardiothoracic ratio of over .50); no enlargement was present in two cases. Posterior displacement of the esophagus, usually not marked, was noted in forty-eight patients, in thirty of whom there was associated systolic expansion of the left auricle. Of the forty-eight patients with an enlarged left auricle eight had associated mitral stenosis. It was observed that the largest left auricles were present in these eight patients.

Electrocardiograms. Electrocardiograms were available for evaluation in ninety-five patients. (Table IV.) In only three patients were the tracings within normal limits. One of these patients was an eighteen year old boy in whom aortic insufficiency had been present for only two months following a traumatic rupture of the aortic valve; the other was an eleven year old girl (group B) with aortic insufficiency who had no symptoms or signs of congestive failure; the third case was a fifteen year old girl with only mild symptoms of failure. Left ventricular hypertrophy was present in ninety-two patients. Eighty-eight of these patients had normal sinus rhythm and four had persistent auricular fibrillation (most of those with auricular fibrillation had associated mitral stenosis). Premature ventricular contractions were common. Varying degrees of AV block (usually first degree) were present in twenty-four patients.

Associated Cardiac Pathology. Rheumatic cases: Eight patients had associated mitral stenosis; six were women and two, men. None of the patients had significant aortic stenosis or tricuspid disease.

Congenital cases: Marfan's syndrome with bicuspid aortic valve was present in one case. Two patients had coarctation of the aorta with probable bicuspid aortic valves (one of these had an aortic arch aneurysm). A bicuspid aortic valve, cerebral berry aneurysm and an abnormal entrance of the superior vena cava into the left auricle were noted in another patient.

Bacterial Endocarditis. In eighteen patients, or 22 per cent of the rheumatic cases, bacterial endocarditis had occurred previously. There were fifteen men and three women. The average age was thirty-one and the average time of onset at which the bacterial endocarditis occurred was 3.6 years prior to this evaluation. Of these eighteen patients four were in group D, ten in group C and four in group B. In five cases the murmur of aortic insufficiency was first observed after the bacterial infection. Two of these cases were associated with increased peripheral symptoms of aortic insufficiency such as jumping carotid artery and pounding in the head; two patients first noted failure after the onset of endocarditis; and the other had the onset of both failure and angina after the infection. In five other patients pre-existing aortic insufficiency became aggravated following the endocarditis. Angina occurred in one of these cases; another patient first experienced failure; in two patients failure became aggravated; and in one both angina and failure first appeared after the endocarditis. Thus in ten of the eighteen patients the occurrence of endocarditis aggravated the pre-existing symptoms of aortic insufficiency or precipitated the signs or symptoms of free aortic insufficiency. We assume that, in these cases, bacterial destruction of the valve occurred with a resultant increased degree of aortic regurgitation.

Two of the four congenital cases with probable bicuspid aortic valves had bacterial endocarditis, one five years and the other nineteen years prior to evaluation. Thus in the entire series of cases 20 per cent had a history of definite bacterial endocarditis.

DISCUSSION

In the past three years at Georgetown University Medical Center we have had the unusual opportunity to evaluate personally over 100 patients with severe aortic insufficiency. Most previous publications on this subject have dealt retrospectively with postmortem material and careful clinical observations have been inadequate in many cases. Previous studies have usually included cases of very mild aortic insufficiency (clinical data such as blood pressures were frequently not given), and other associated valvular defects were the predominant lesion. Also, most reports have dealt exclusively or almost exclusively with the specific problem of syphilitic aortic insufficiency. With effective antibiotic and public health measures, syphilitic cardiovascular disease is becoming less and less of a problem and rheumatic valvular disease is assuming more importance.

The two features of the present study which should be borne in mind are the predominance of rheumatic aortic insufficiency in this series (83 per cent) and the inclusion of cases with

only "severe" degrees of aortic insufficiency. Because of the small number of cases of syphilitic, congenital and traumatic etiology, valid statistical information about these groups cannot be obtained from this study. The following discussion and conclusions will relate, therefore, mainly to aortic insufficiency of rheumatic etiology. Undoubtedly the great preponderance of cases of rheumatic origin in this series is due in part to geographic location and case selection, and is not a true index of its relative frequency. In both the rheumatic and syphilitic groups the predominance of men was significant. As might be expected, severe aortic insufficiency below the age of forty was more likely to be of rheumatic than syphilitic etiology.

The average rheumatic patient with aortic insufficiency is typified by the following profile history (Fig. 3): acute rheumatic fever at age thirteen with recurrent episodes in subsequent years; hemodynamically significant aortic insufficiency present by the age of twenty; asymptomatic until approximately the age of thirty. The final or "symptomatic" stage was usually first manifested by mild dyspnea on exertion or a sensation of increased cardiac thrust. In some instances angina pectoris was the first symptom of myocardial disability but this usually occurred a few years after the onset of dyspnea on exertion. In our experience peripheral edema, orthopnea and paroxysmal nocturnal dyspnea occurred relatively late in the course of aortic insufficiency, and indicated a graver prognosis. (Fig. 5.) Hemoptysis was not observed in any patient with pure aortic insufficiency; in those few patients in whom it did occur there was associated mitral stenosis. Peripheral edema was likewise rare in this group of patients and usually followed a long period of left ventricular failure.

It should be emphasized that moderately severe aortic insufficiency may be present for many years with no evidence of cardiac decompensation or disability, and in a few patients this "asymptomatic" period may extend for as long as twenty to thirty years.

Once symptoms of failure or angina pectoris develop, the patient may be relatively comfortable for several years. In fact sixteen of the eighty-two rheumatic patients had symptoms of congestive failure for more than ten years. Likewise, angina pectoris may be present for years, either alone or associated with congestive failure.

Cardiac decompensation in patients with rheumatic aortic insufficiency may be related both to rheumatic activity and to the cardiac burden imposed by aortic incompetency. Recurrent episodes of rheumatic activity may account for the frequent exacerbations of congestive heart failure which occurred in several of our patients over a period of many years. On the other hand, patients with syphilitic aortic insufficiency have cardiac embarrassment secondary to two irreversible pathologic situations: (1) aortic incompetency secondary to dilatation of the aortic ring and separation of the aortic valve commissures and (2) coronary insufficiency secondary to syphilitic coronary ostial involvement. Thus in syphilitic aortic insufficiency one would not expect symptomatic remissions and exacerbations which are so characteristic of the rheumatic group, and the clinical course is rapidly and progressively downhill.

Angina pectoris was present in almost 50 per cent of the rheumatic cases. It was interesting to observe that the average age of those patients with and without angina was the same. Usually the classic picture of substernal distress related to physical or emotional excitement was present. Nocturnal angina was fairly common and in several cases was the predominant form present. Autopsies have now been performed in a number of patients with aortic insufficiency with angina pectoris and in none has any evidence of coronary artery disease or coronary ostial narrowing been found. Since a large portion of coronary blood flow occurs during diastole, angina might be explained by three mechanisms: (1) marked lowering of diastolic pressure with resultant decrease in coronary artery blood flow, (2) the "sucking" action of the regurgitant stream on the coronary arteries (Bernouilli's principle) and (3) relative coronary insufficiency related to the large left ventricular mass. Whatever the mechanism, we wish to emphasize the frequency of angina pectoris in patients with severe aortic insufficiency of rheumatic etiology. This is in contrast to reports in the literature stressing the rarity of angina pectoris in rheumatic aortic insufficiency, and its relative frequency in the syphilitic group.

The most significant physical findings were the low diastolic blood pressure and classic peripheral signs of free aortic insufficiency. Every patient had an aortic diastolic murmur (usually grade 4), an aortic systolic murmur (usually grade 3), an apical systolic murmur (usually

grade 3) and a ventricular gallop followed by an Austin Flint rumble.

Worthy of emphasis is the fact that an aortic systolic murmur was present in all of our cases. The average intensity of this murmur was grade 3 but in many instances the murmur varied from grade 4 to grade 6 and often was associated with a systolic thrill. Clinically significant aortic stenosis was not considered to be present in any instance, and in cases in which autopsies were performed significant aortic stenosis was not found. Therefore, we have established the general rule that the presence of severe aortic insufficiency characterized by a low diastolic pressure virtually precludes the existence of significant aortic stenosis. Hepatomegaly occurred in over 50 per cent of the cases. Pulmonary rales, splenomegaly and peripheral edema were relatively uncommon.

Since all the patients demonstrated a ventricular diastolic gallop and an apical diastolic rumble (Austin Flint) it is difficult to select those patients who have only pure aortic insufficiency from those who have associated mitral stenosis. The following clinical points are of value in this respect. Mitral stenosis was three times more common in women than men. In those patients with "pure" aortic insufficiency, M1 * was usually not accentuated, the third heart sound had the timing of a ventricular diastolic gallop (usually .14 second or longer after the second heart sound), and the diastolic rumble was located in the early and mid-portion of diastole. In contrast, those patients with associated mitral stenosis demonstrated a loud M1, an opening snap and a rumble which usually had a presystolic component. In addition, auricular fibrillation usually indicated associated mitral stenosis. Although posterior displacement of the esophagus by x-ray study occurred in approximately 50 per cent of the entire series, the most marked posterior displacement indicative of an enlarged left auricle usually was associated with mitral stenosis. Calcification of the mitral valve area was a valuable sign in indicating associated mitral stenosis. Electrocardiograms in patients with "pure" aortic insufficiency usually demonstrated a horizontal electrical axis and evidence of left ventricular hypertrophy whereas a vertical electrical axis and prominent P waves were often associated with mitral stenosis.

Three per cent of the patients in this series had associated coarctation of the aorta. The clinical clue in each instance was a systolic blood pressure in the lower extremities equal to or lower than that in the upper extremities. This is in marked contrast to the usual finding in aortic insufficiency of a systolic blood pressure in the lower extremities markedly higher than that in the upper extremities (Hill's sign). In contrast to the classic picture of coarctation of the aorta, palpation of the femoral, dorsalis pedis and posterior tibial pulses in cases of aortic insufficiency with coarctation revealed good or even increased pulsations because of the wide pulse pressure present. Therefore, blood pressures should be carefully recorded in the arms and legs of all patients with aortic insufficiency in order to detect those with associated coarctation of the aorta.

Of particular interest was the high frequency of posterior esophageal displacement in forty-eight of the cases and systolic expansion of the left auricle in thirty. Although this is usually thought to be due to an enlarged left auricle, we believe that the marked enlargement of the left ventricle present in almost all of our cases was responsible for posterior esophageal displacement in many instances. The electrocardiographic pattern in those cases with "pure" aortic insufficiency almost always revealed normal sinus rhythm and left ventricular hypertrophy. First degree AV block was present in approximately 25 per cent of the cases.

Bacterial endocarditis was relatively common, occurring in eighteen of the eighty-three rheumatic patients. Of significance is the fact that in ten of these eighteen patients the signs and/or symptoms of aortic insufficiency first became apparent or became aggravated following the bacterial infection. Therefore, in any patient with severe aortic insufficiency, particularly in those with progressive signs and/or symptoms of cardiac decompensation, the coexistence of bacterial endocarditis should be suspected and ruled out by appropriate studies. Frequently, following bacterial endocarditis the course of congestive heart failure is rapidly downhill; therefore, these patients might be good candidates for consideration of surgical correction of the aortic insufficiency.

Two important factors in prognosticating the clinical course of a patient with severe rheumatic aortic insufficiency are the age of the patient and the duration of existing symptoms. It is impossible to generalize but it would appear that a patient in group C approximately age

* First sound at the mitral area.

thirty-four who has been symptomatic for three or four years may be expected to progress to a group D classification in the next two or three years. In general, the association of angina with congestive failure bears a graver prognosis, and in our experience these patients have been more severely incapacitated. Of the thirty-two patients with both angina pectoris and congestive failure about 40 per cent were in group D whereas only 16 per cent of those with congestive failure or angina pectoris alone were in group D.

Approximately 5 per cent of the patients with severe aortic insufficiency, fairly well compensated died suddenly and unexpectedly. It has been assumed that death was due to paroxysmal ventricular fibrillation, although we have no definite proof of this. Ventricular premature beats were common in this group.

Although some reports state that medical treatment of aortic insufficiency is of little value when signs or symptoms of failure begin,[15,21,24] others indicate that patients may respond initially quite as well as with other types of heart disease.[6] Our clinical impression has been somewhat between these two extremes. Some have been greatly benefited and are kept in a fairly stable state of compensation for a number of years on medical therapy; others have progressed quite rapidly once failure has occurred, death ensuing in a matter of months. Our evaluation supports the general belief in the literature that once congestive failure develops in syphilitic aortic insufficiency the course is more rapidly downhill than in the rheumatic group. The average rheumatic patient was symptomatic for 6.4 years, the average syphilitic patient 2.5 years.

Public health measures and early therapy of syphilis are rapidly reducing the incidence of syphilitic aortic insufficiency. It is quite conceivable that more vigorous therapy of hemolytic streptococcal infections and prophylactic antibiotic therapy in rheumatic patients will significantly reduce the incidence and severity of rheumatic valvular disease. Until preventive measures eliminate valvular disease, it is important that we be familiar with the natural clinical course of these lesions so that we might better be able to select those patients who will benefit from surgical intervention. The prognosis in aortic insufficiency is most grave following the sudden onset of severe aortic incompetency related to rupture or inversion of the aortic valves. This might occur following bacterial endocarditis, direct or indirect trauma to the chest, severe effort or, spontaneously, in syphilitic cardiovascular disease.

SUMMARY AND CONCLUSIONS

The clinical features in 100 cases of severe aortic insufficiency are reviewed. Eighty-three cases were rheumatic, twelve syphilitic, four congenital and one traumatic. The average age of patients was thirty-four years.

The natural clinical course of rheumatic aortic insufficiency and syphilitic aortic insufficiency are compared. The progression of symptoms in syphilitic aortic insufficiency was twice as rapid as in the rheumatic group. In the rheumatic group, the average patient had rheumatic fever at age thirteen, developed hemodynamically significant aortic insufficiency at age twenty, and noted symptoms at age thirty. The symptomatic period ranged from two months to thirty years, averaging 6.4 years.

Cardiac palpitation and dyspnea on exertion were the earliest and most frequent symptoms in aortic insufficiency of any etiology. Angina pectoris occurred in almost 50 per cent of the rheumatic group. This was not related to coronary artery disease or to coronary ostial involvement.

The average blood pressure was 155/37 mm. Hg. An aortic systolic and diastolic murmur, apical systolic murmur, ventricular diastolic gallop and Austin Flint murmur were present in every case. Hepatomegaly occurred in over 50 per cent of the cases.

Radiologic findings included left ventricular enlargement, aortic "jump" and "rocking" motion of the heart. Posterior displacement of the esophagus occurred in approixmately 50 per cent of the patients and 60 per cent of these had systolic expansion of the left auricle.

Electrocardiograms usually demonstrated normal sinus rhythm, left ventricular hypertrophy and, frequently, first degree AV block. Auricular fibrillation or a vertical electrical axis with large P waves often indicated mitral stenosis.

Bacterial endocarditis had occurred in 22 per cent of the rheumatic group and was frequently followed by progressive cardiac decompensation.

The following factors indicated a poor prognosis: (1) recent occurrence of bacterial endocarditis with subsequently increasing signs of aortic insufficiency: (2) coexistence of angina pectoris and congestive heart failure; (3) syphilitic etiology; (4) marked cardiomegaly; (5) in-

creasing age (over 40) and/or increasing duration of symptoms.

Our experience, like that of others, indicates that patients with "free" aortic insufficiency often remain asymptomatic for many years. Congestive failure and/or angina pectoris frequently were present for many years, often with remissions and exacerbations which were related to rheumatic activity. Some patients were maintained for years on conservative medical management but usually progressive failure occurred.

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Fatal Pulmonary Insufficiency Due to Radiation Effect upon the Lung*

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FIBROSIS of the lung as a result of x-ray radiation has become a well established clinical entity. This is usually a complication of the x-ray therapy of mammary carcinoma[1–3] but may also occur with treatment for carcinoma of the lung,[3–5] carcinoma of the esophagus[2,3] and pulmonary lymphoma.[6,7]

The extent of pulmonary fibrosis following radiation reaction in the lung is ordinarily not of clinical significance. Occasionally severe pulmonary insufficiency develops after radiation. The exact nature and degree of these disturbances has been inadequately elucidated and only limited data correlating lung function and pathology are available.

It is the purpose of this paper to indicate that severe disturbances of pulmonary function characterized by "alveolar-capillary block" may occur with extensive radiation-induced fibrosis of the lung, and further that these pulmonary functional changes may lead to a rapidly fatal termination. Five patients who received radiation therapy for malignant disease of the lung or mediastinum are reported, and the clinical course is correlated with alterations in pulmonary function and with the pathologic anatomy. In two of the patients, detailed pulmonary function studies were performed; in the remainder the arterial blood gases were studied in all but one patient during the acute phase of illness. Radiation therapy data in these five patients are summarized in Table I.

METHODS

Pulmonary function studies were performed using the standardized technics outlined by Baldwin et al.[8] for lung volumes, ventilation, exercise response, maximum breathing capacity and arterial blood gases. The analyses of gas tensions and calculation of the alveolar-arterial oxygen gradients on room air and low oxygen mixtures were performed by the technics

TABLE I
SUMMARY OF RADIATION FACTORS

	Case I	Case II	Case III	Case IV			Case V				
Date				Dec. 1954	Aug. 1955†	Sept. 1955‡	May 1953	May 1954	Jan. 1955	May 1955	Aug. 1955
Radiation factors:											
Kilovolts	250	1,000	1,000	1,000	1,000	1,000	250	250	250	1,000	1,000
Target skin distance (cm.)	50	70	70	70	70	70	50	50	50	70	70
Milliamperes		3	3		3	3	15	15	15	3	3
Filter	0.5 of copper (plus 1 of aluminum)	1 mm. lead	1 mm. lead		1 mm. lead	1 mm. lead	Thoreaus	Thoreaus	Thoreaus	1 mm. lead	1 mm. lead
Half-value layer	2 of copper	3.9 mm. lead	3.9 mm. lead	3.6 mm. lead	3.9 mm. lead	3.9 mm. lead	3.0 mm. lead	3.0 mm. lead	3.0 mm. lead	3.9 mm. lead	3.9 mm. lead
Daily dose to the depth (in roentgens)	123	200	300		200	200				170	200
Number of treatments/ total no. days	15/20	30/43	10/14	/51	18/30	20/30	/28	/42	/22	12/18	20/23
Total depth dose in roentgens	4,100	6,000	3,200	4,477	1,800	2,000	2,700	2,714	3,135	2,064	2,000

† Right lung.
‡ Left lung.

* From the Chest Medical Service and the Cardiopulmonary Laboratory of the Veterans Administration Hospital, Bronx, New York.

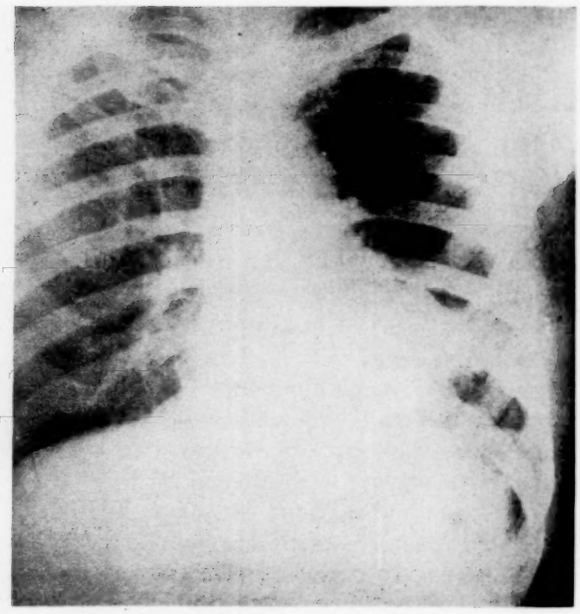

FIG. 1A. X-ray taken before radiation therapy, Case I.

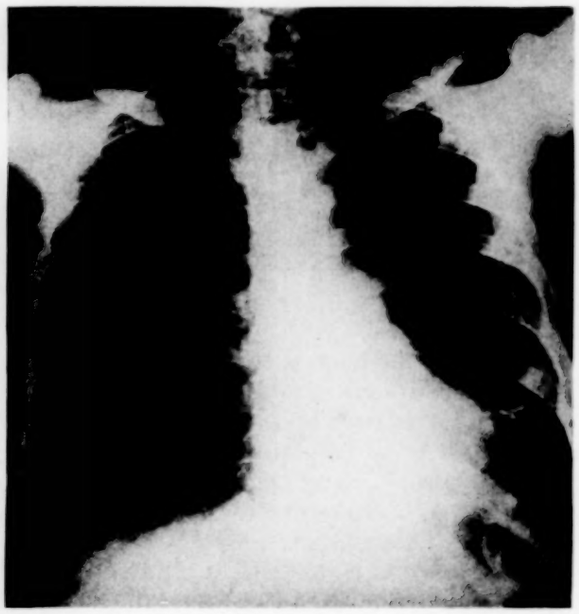

FIG. 1B. Seventeen days after completion of radiation therapy, Case I.

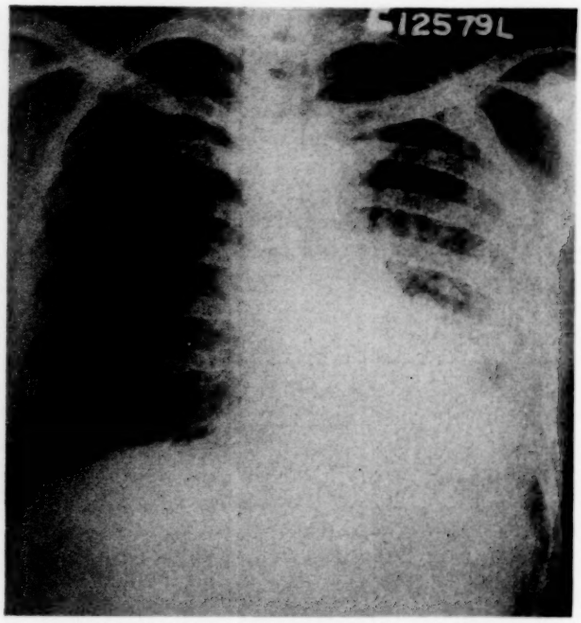

FIG. 1C. Film taken on admission to this hospital three weeks after completion of radiation therapy, Case I.

described by Lilienthal, Riley and others.[9] Analysis of expired air for carbon dioxide and oxygen was made with the micro-Scholander apparatus. Direct pH measurements of the arterial blood were performed with the Cambridge research pH meter. Carbon dioxide tensions were calculated also by means of the Henderson-Hasselbalch equation.[10] The correlation between the calculated pCO_2 and the directly measured result utilizing the bubble technic was sufficiently close to minimize any error in the gradient calculations. In cases II, III and V the patients were too ill to tolerate complete studies and it was only possible to measure the blood gases at the bedside. Every effort, however, was made to permit the development of a steady state before duplicate specimens were withdrawn for analysis.

CASE REPORTS

CASE I. This forty-eight year old Negro freight handler was admitted to the Bronx V. A. Hospital (No. 185 570) for the first time on October 1, 1954, complaining of cough of four to five months' duration together with weakness and shortness of breath for two and a half months. On August 4, 1954, he had entered another hospital because of three months of generalized pruritus. Painless swelling in the right groin had been present for three years. A productive cough developed two months prior to that admission and malaise was also noted.

Physical examination revealed maculopapular pigmented lesions over the arms and chest, and generalized adenopathy with rubbery, firm, painless nodes varying in size from ½ cm. to an 8 by 9 cm. node in the inguinal region. Posteriorly and to the left of the spine in the region of T6 to T8, an area of bronchophony and bronchial breath sounds was noted. The liver was enlarged two to three fingerbreadths below the costal margin. The prostate was symmetrically enlarged. There was clubbing of the extremities. The x-ray taken on admission (Fig. 1A) revealed an infiltrative process in the left lower lung field. Laboratory data included a hemoglobin of

TABLE II

PULMONARY FUNCTION STUDIES

A. Lung Volumes and Ventilation

	Lung Volumes (% of predicted)			$\frac{RA}{TC} \times 100$	Alveolar N_2 (after 7 min. O_2)	Maximum Breathing Capacity (% of predicted)	Ventilation (L./min./sq. M.)		
	Vital Capacity	Residual Air	Total Capacity				Basal	Exercise	First Minute Recovery
Normal	100	100	100	<30	<2.5	100	<4.0	<10.0	<12.0
Case I	37	95	57	41	2.85	50	6.3	10.5	15.8
Case IV	22	20	23	18	1.02	38	6.5	8.7	18.2

B. Oxygen Consumption and Gas Exchange

	O_2 Consumption (cc./min./sq. M.)		Arterial O_2 Saturation (%)			Arterial CO_2 Content (vol. %)	Room Air					Low Oxygen				
	Basal	Exercise	Basal	Exercise	Low O_2		Arterial pCO_2 (mm. Hg)	Alveolar pO_2 (mm. Hg)	Arterial pO_2 (mm. Hg)	A-A Grad. (mm. Hg)	Dead Space (% T.A.)	Arterial pCO_2 (mm. Hg)	Alveolar pO_2 (mm. Hg)	Arterial pO_2 (mm. Hg)	A-A Grad. (mm. Hg)	Dead Space (% T.A.)
Normal	129 ± 13	480 ± 74	96 ± 2	96 ± 2	....	48 ± 4	35–40	100	90–100	<12	<30%	35–40	..	..	<12	<30%
Case I	147	272	96.4	71.7	81	49.7	39	102	85	17	46	34	69	50	19	43%
Case IV	139	145	89.3	65.8	73.5	44.5	32	111	62	49	38%	24	77	40	37	36%

15 gm. per cent, a white blood count of 8,400 with a normal differential, blood urea nitrogen of 11 mg. per cent, alkaline phosphatase 3.7 Bodansky units, albumin 3.7 gm. per cent, globulin 4.3 gm. per cent, BSP 40 per cent retention in thirty minutes, and a sedimentation rate of 102 mm. per hour. The platelet count was 264,000.

On bronchoscopy, a fungating tumor was discovered in the lumen of the left lower lobe bronchus. The biopsy specimen revealed epidermoid carcinoma, grade 2. In addition, a lymph node biopsy specimen revealed Hodgkin's disease. Because of the presence of Hodgkin's disease it was decided to employ radiation rather than surgery. Therefore, three 10 by 13 cm. portals (anterior, posterior and left lateral) were radiated each day for fifteen days during the period August 18th to September 7th. The total tumor dose was 4,100 r. (Fig. 1B.) Prior to discharge on August 20th a course of nitrogen mustard, 0.4 mg./kg. of body weight, was given.

Within two weeks following completion of radiotherapy the patient noted progressively severe exertional dyspnea, marked increase in productive cough and extreme fatigue and lassitude. The symptoms necessitated admission to the Bronx V. A. Hospital. Physical examination at the time of admission revealed a chronically ill Negro man who evidenced marked weight loss and a temperature of 102°F. Blood pressure bilaterally was 95/65 with a pulse rate of 100. The trachea was in the midline. The heart was not enlarged and A2 was greater than P2. Fremitus was increased over the left mid-lung field posteriorly with slight dulness in that area and at the left base. Crepitant rales were heard over the left anterior chest and in the axilla. The liver was enlarged three fingerbreadths below the right costal margin. There was a nodular mass in the right lower quadrant just above the inguinal ligament and there were several small cervical nodes bilaterally. The femoral and inguinal nodes were markedly enlarged. Neurologic examination was within normal limits. X-ray taken on admission (Fig. 1C) revealed extensive bilateral infiltrative disease interpreted as radiation reaction. Laboratory data included a hemoglobin of 12 gm., white blood count of 12,800 with a normal differential, and a corrected sedimentation rate of 28 mm. per hour. Cultures of sputa were negative for tubercle bacilli. Two blood cultures gave negative results. Pulmonary function studies were performed on October 27th and 28th. The data obtained are shown in Table II.

The patient's early course was characterized by

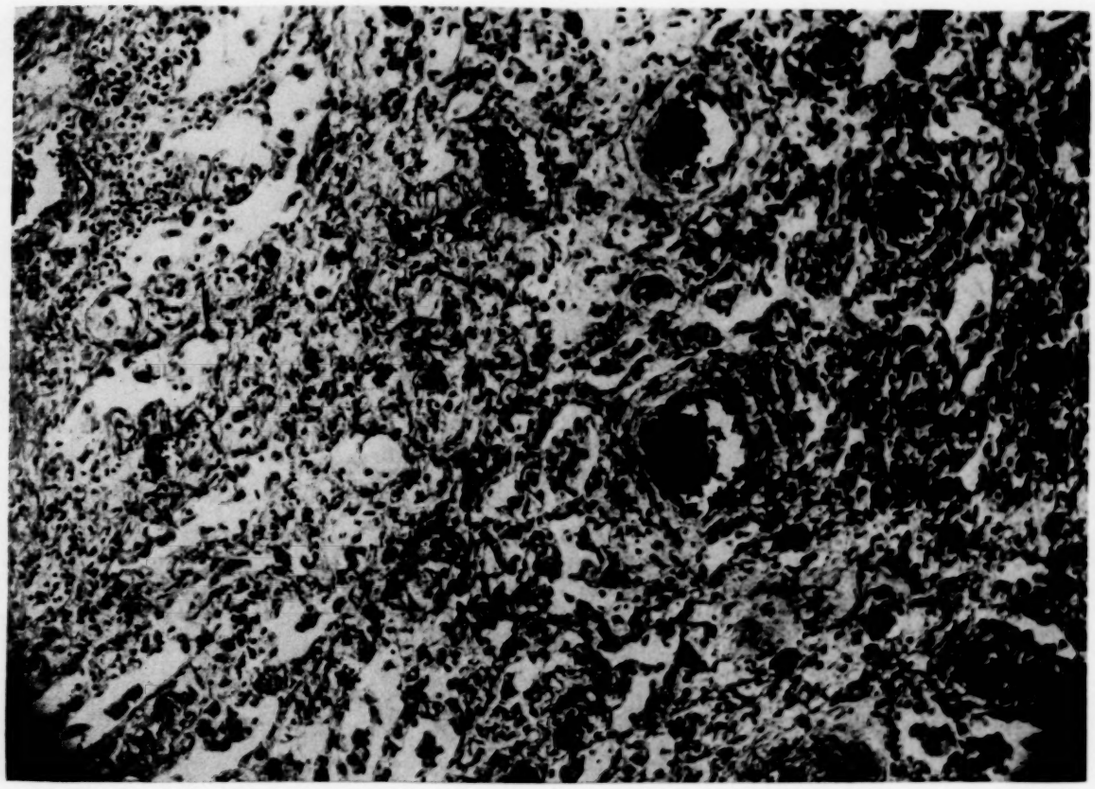

FIG. 2A. Microscopic section from the left upper lobe, Case 1.

daily temperature elevations to 102°F., which responded to penicillin therapy. The most striking symptom noted by the patient was gradually increasing dyspnea on effort, progressing to dyspnea at rest. Repeated physical examination revealed bronchial breathing, whispered pectoriloquy and posttussive rales over the left side of the chest posteriorly; an intermittent friction rub was heard anteriorly. A gradual increase in the intensity of the second pulmonic sound was noted.

Bronchoscopy performed on October 12th revealed an entirely normal tracheobronchial tree with no evidence of the tumor mass previously reported at the other hospital.

On October 29th the patient suffered repeated convulsive episodes involving the left side of the body with gradually increasing left hemiparesis. Severe dyspnea and productive cough characterized the last ten days of life. A course of nitrogen mustard, 0.4 mg./kg. of body weight, given a few days before death on November 12th did not alter the patient's course.

Autopsy was performed twenty-three hours after death. There was scaliness of the skin over the anterior left side of the chest corresponding to the site of x-ray radiation. The heart weighed 490 gm. and significant right ventricular hypertrophy was present. The left lung was firm in consistency with fine bands of fibrous tissue showing through the cut surface, especially in the lower lobe. The right lung revealed similar fibrotic changes but to a lesser degree. The bronchial lumen at the site from which the original biopsy specimen was taken showed no evidence of carcinoma. Metastatic carcinoma was observed in the brain. Numerous tumor nodules were apparent in the liver.

Microscopically, diffuse interstitial and intra-alveolar fibrosis of the entire pulmonary parenchyma was observed, most marked in the areas directly beneath the radiation portals on the left. (Fig. 2A.) Similar findings of lesser degree were observed in the right lung. (Fig. 2B.) Thickening of alveolar walls and pulmonary blood vessels was observed, and the pulmonary blood vessels showed thrombosis with organization of some of the larger branches. A marked increase in the fibrous tissue surrounding bronchi and bronchioles was observed. The bronchial epithelium in many areas was desquamated with loss of some cilia. There were many smaller bronchioles with intact epithelium and with preservation of cilia; in general, the changes in the bronchioles were much less severe than the changes within alveoli. Pleural fibrosis was present. The only tumor tissue noted was a small patch of cells on the mucosal surface of the left lower lobe bronchus and a tumor metastasis in a left lower lobe lymphatic vessel. Hodgkin's disease was present in the liver and lymph nodes.

FIG. 2B. Microscopic section from the right lower lobe, Case I.

The gross and histologic changes in the lungs were considered to be typical of severe radiation reaction with fibrosis.

CASE II. This sixty-one year old white man with a history of long-standing mild productive cough was admitted to the V. A. Hospital, Bath, New York, complaining of recent weight loss, anorexia and an increase in cough. Minimal exertional dyspnea was present. Because of this history and the x-ray findings, bronchoscopy was performed on April 29, 1954. A biopsy specimen taken during this procedure was inconclusive and the patient was admitted to the Bronx V. A. Hospital (No. 180 071) on May 12, 1954.

The patient was in no acute distress. Chest examination revealed dulness on percussion, decreased fremitus and absent breath sounds over the upper one-third of the left hemithorax. In addition there was evidence of mild pulmonary emphysema. The remainder of the physical examination, including examination of the heart, was within normal limits. X-ray (Fig. 3A) on June 4th revealed a mass in the left lung root and a ground-glass opacification of the left upper lobe.

Bronchoscopy on June 22nd revealed the left upper lobe orifice to be occluded at its point of origin from the main stem bronchus. A biopsy specimen of the tissue found along the inferior border of the left upper lobe orifice disclosed anaplastic epidermoid carcinoma. On June 29th radiotherapy was instituted through 11 by 15 cm. anterior and posterior portals. The patient thereafter experienced marked clinical improvement with a decrease in cough and sputa. After 2,200 r were given marked clearing in the chest x-ray film was apparent. (Fig. 3B.) The total tumor dose of 6,000 r was completed on August 12th. Two days later the patient experienced an acute episode characterized by temperature elevation to 105°F., severe dyspnea and hyperventilation, as well as increased cough productive of mucoid sputum. Diaphoresis and marked weakness were also present. Physical examination at this time revealed the patient to be in marked respiratory distress, utilizing accessory muscles of respiration, at a respiratory rate of 40 per minute. Marked cyanosis was present. Physical examination of the chest was essentially unchanged save for the appearance of bilateral basal rales. The clinical and the x-ray findings suggested the possibility of an acute radiation effect on the lung. The patient was too acutely ill to undergo complete pulmonary function studies but an arterial blood study on August 20th revealed a partial pressure of carbon dioxide of 26 mm. Hg, a partial pressure of oxygen of 61 mm. Hg and a pH of 7.47. The carbon dioxide content was 39.2 vol. per cent, the oxygen content was 13.5 vol. per cent, the oxygen capacity was 14.8 vol. per cent, the arterial oxygen saturation was 91 per cent. X-ray (Fig. 3C) on August 24th revealed

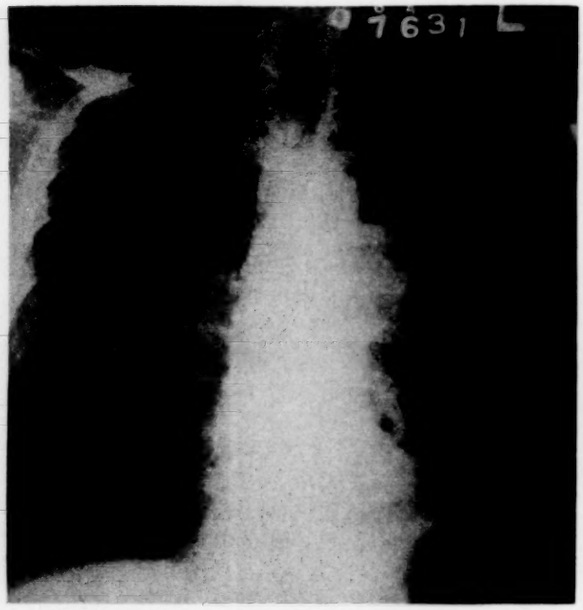

FIG. 3A. Film taken on admission to this hospital, Case II.

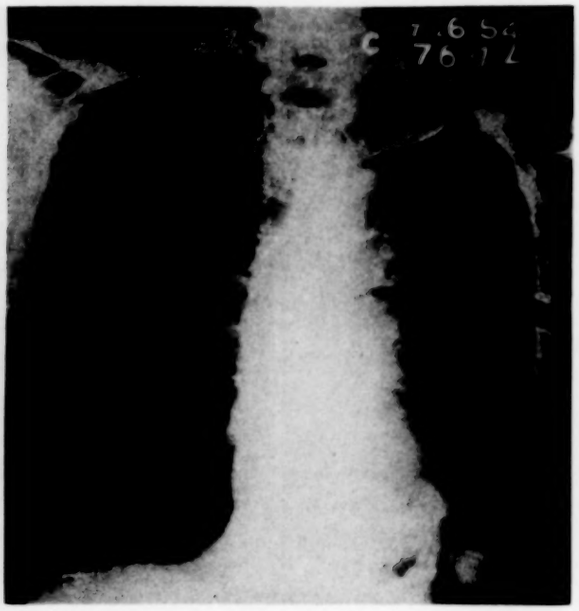

FIG. 3B. X-ray after 2,200 roentgens to the tumor, Case II.

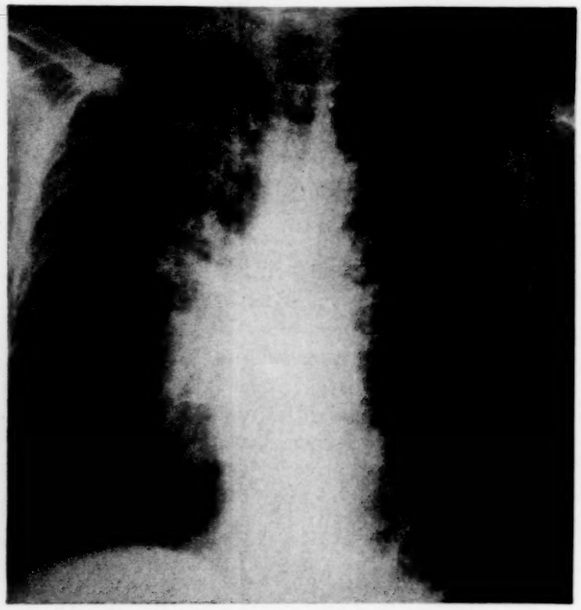

FIG. 3C. X-ray taken twelve days after completion of radiation therapy, Case II.

bilateral infiltrative disease interpreted as radiation reaction.

The patient's dyspnea and high fever did not respond to various antibiotics. On August 20th hydrocortisone, 200 mg. by mouth per day, was started together with aqueous penicillin. The temperature reached normal on August 22nd and the patient was afebrile for three days during which time the penicillin was discontinued and the hydrocortisone decreased to 100 mg. per day. Three days later a spiking fever to 101°F. suddenly developed and the hydrocortisone was increased to 200 mg. per day once again. Despite this, the temperature continued to range between 102° and 103°F. so that on September 1st ACTH gel, 20 mg. per day, was instituted. Hydrocortisone and ACTH were discontinued on September 6th because of lack of response. The patient remained moderately febrile and slowly went downhill with a course characterized by severe and progressive dyspnea, cyanosis and cough. He died on October 4th, approximately three weeks after the onset of the acute symptomatology.

Autopsy was performed fifteen hours after death. The significant findings were confined to the respiratory system. The upper lobes of both lungs had an extremely firm consistency. The parenchyma in these areas was blue-gray in appearance, extremely fibrotic and sharply demarcated from the other lobes of both lungs. Numerous emphysematous bullae were apparent in the fibrotic areas. The lower lobes revealed moderate congestion bilaterally. The bronchus to the left upper lobe was ulcerated and infiltrated with white firm tissue. A firm node was noted inferior to this bronchus. Metastatic carcinoma was apparent in the right kidney, right adrenal and an axillary lymph node.

Microscopically, an extensive necrotic tumor was noted in the bronchus to the left upper lobe. Sections of the right and left upper lobes (Fig. 4A) revealed thickened pleura and extensive interstitial and peribronchial fibrosis. Intra-alveolar fibrosis was apparent together with extensive intra-alveolar foci of hyaline material with admixture of fibroblasts. There was marked reduction in the number of alveoli as well as congestion and thickening of the interalveolar septa. Marked capillary proliferation was present and the smaller pulmonary arteries showed

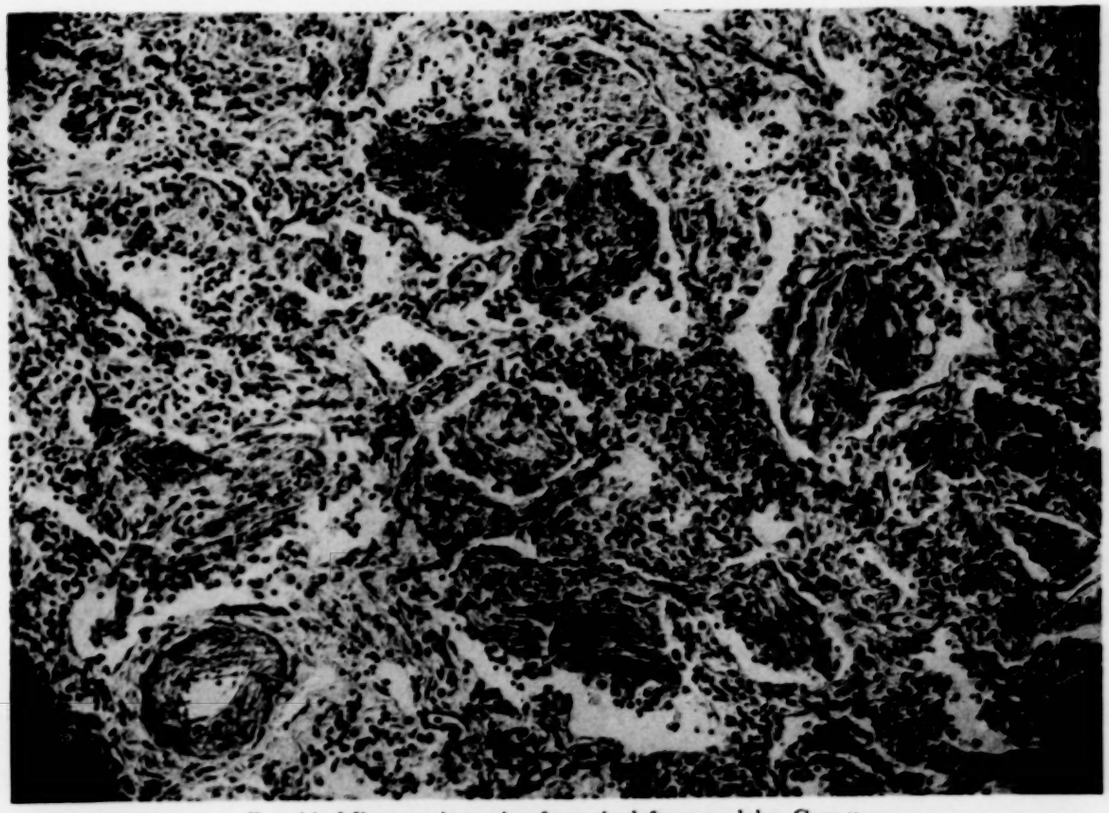

FIG. 4A. Microscopic section from the left upper lobe, Case II.

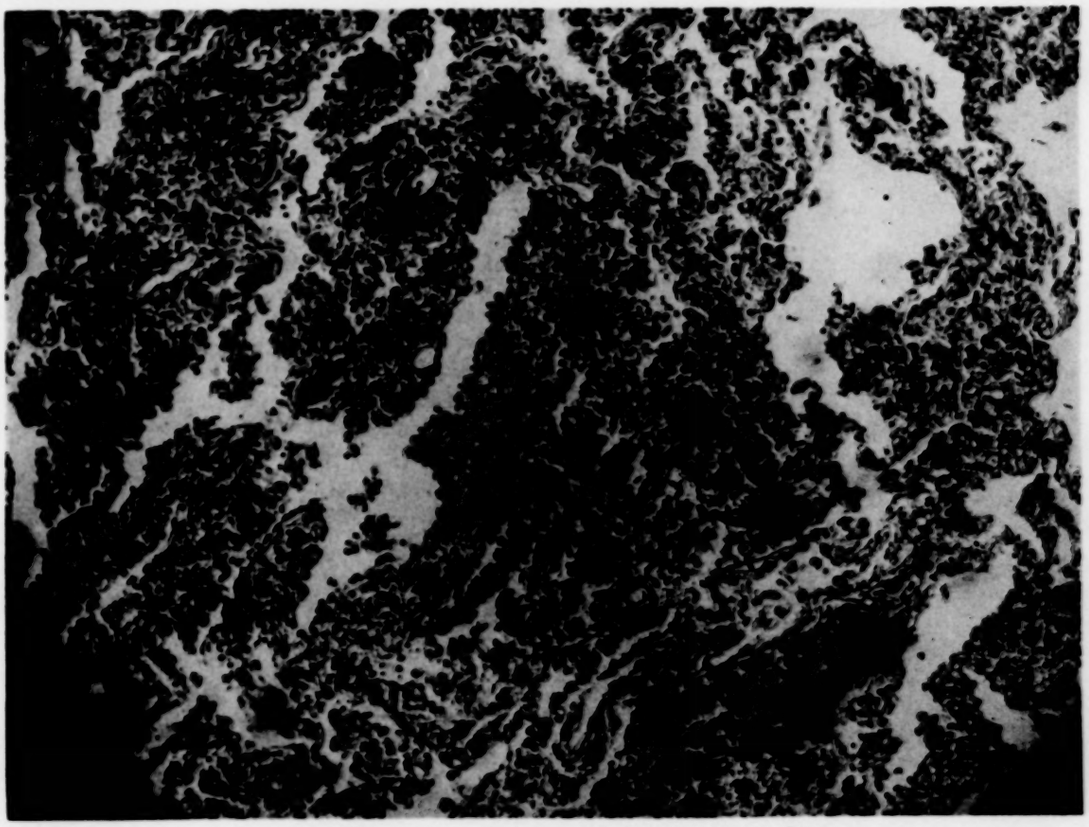

FIG. 4B. Microscopic section from the left lower lobe, Case II.

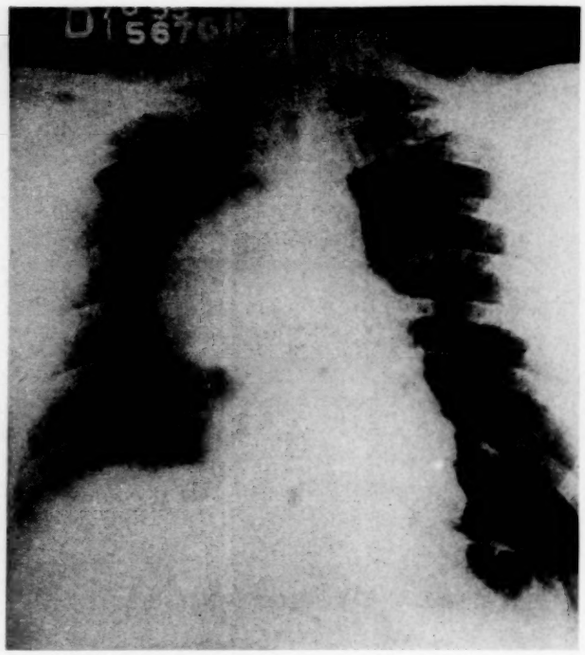

FIG. 5A. X-ray taken before radiation therapy, Case III.

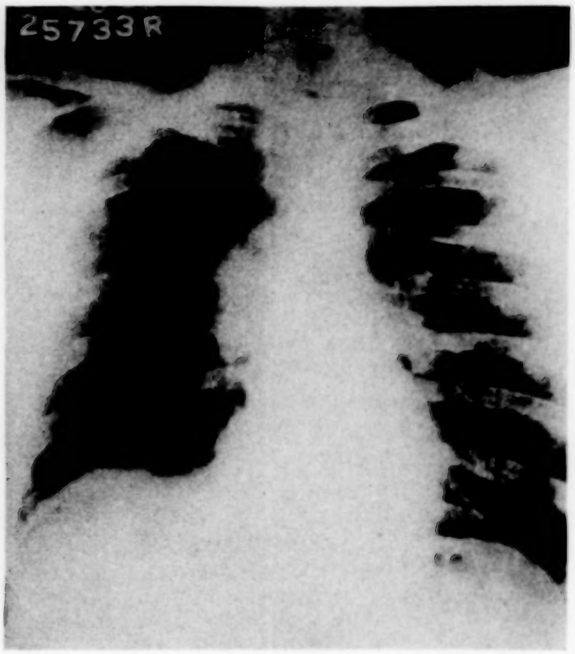

FIG. 5B. X-ray taken one week after completion of radiation therapy, Case III.

thickening and occasional hyalinization of the intima. The mucosa of the bronchioles was disrupted in many areas. The lower lobes revealed similar (Fig. 4B) although less advanced changes. The heart was not enlarged.

The findings in the lung were considered to be chiefly the result of severe radiation reaction.

CASE III. This twenty-five year old white man was first admitted to the Bronx V. A. Hospital, (No. 200 866) in October, 1950. Right orchidectomy was performed, and a microscopic diagnosis of teratocarcinoma with embryonal carcinoma was made.

In June, 1953, x-rays of the chest revealed for the first time a right anterior paracardiac mass. This progressively enlarged, and in January, 1955, thoracotomy revealed metastatic testicular embryonal carcinoma involving a portion of the anterior segment of the right upper lobe and adjacent mediastinum. The mass was resected.

Recurrence of the mass was noted postoperatively. (Fig. 5A.) On July 6th radiation therapy was begun through an anterior and a posterior 18 by 18 cm. portal, with a daily dose of 300 r to the depth. Radiotherapy was completed on July 19th after a total dose of 3,200 r. X-rays of the chest at this time (Fig. 5B) showed some regression of the mass.

On September 30th, ten weeks after the completion of radiotherapy, the patient noted the acute onset of cough, frothy sputum and dyspnea. X-ray of the chest (Fig. 5D) at the time was compatible with bilateral radiation reaction. It is of interest that ten days previously the x-ray (Fig. 5C) had shown only some haziness in the region of the right lower lobe. The patient's symptoms progressed rapidly. On October 3rd administration of prednisone, 20 mg. per day, was begun. Five days later chills and fever to 101°F. developed; prednisone was stopped and tetracycline begun. The patient's condition became worse and he was readmitted on October 10th.

Physical examination at that time revealed a dyspneic and cyanotic white man. The temperature was 101.8°F., with a pulse rate of 120 and a respiratory rate of 24. Bronchial breath sounds with many fine rales were heard bilaterally, more prominently on the right. The pulmonic second sound was booming. Movements of the thoracic cage appeared normal. The hemoglobin, white blood cell and differential counts, urinalysis, blood urea nitrogen and liver function tests were within normal limits. The electrocardiogram was normal at first but later revealed S-T segment depression in the left precordial leads. The patient was too ill to tolerate any pulmonary function study. He was treated with oxygen and antibiotics. Steroid therapy was reinstituted during the last two days of life. His temperature ranged between 100° and 103°F. He failed rapidly in spite of therapy and died on October 23rd, three weeks after the onset of acute symptomatology.

Autopsy was performed twenty-eight hours after death. An extensive organizing mural thrombus was present, attached to the endocardial surface of the right ventricle. The heart was otherwise normal. The right lung was firm, and cut section revealed a large fan-shaped area of fibrosis extending out into the parenchyma from the perihilar area. The remainder

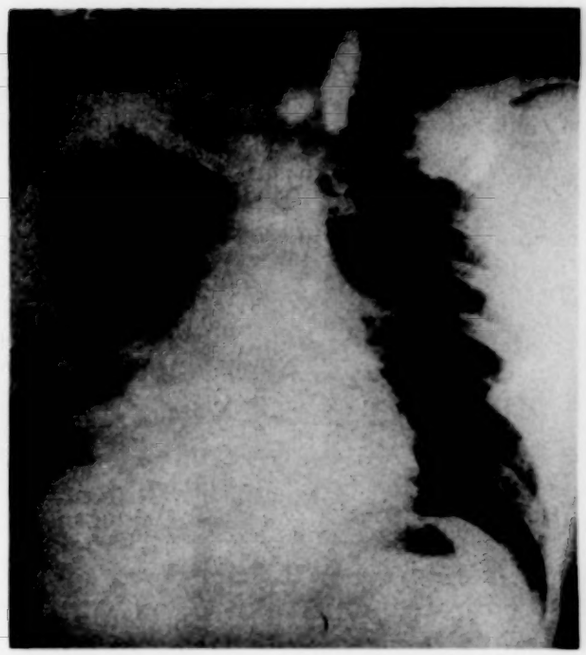

FIG. 5C. X-ray taken ten days prior to onset of acute symptoms, Case III.

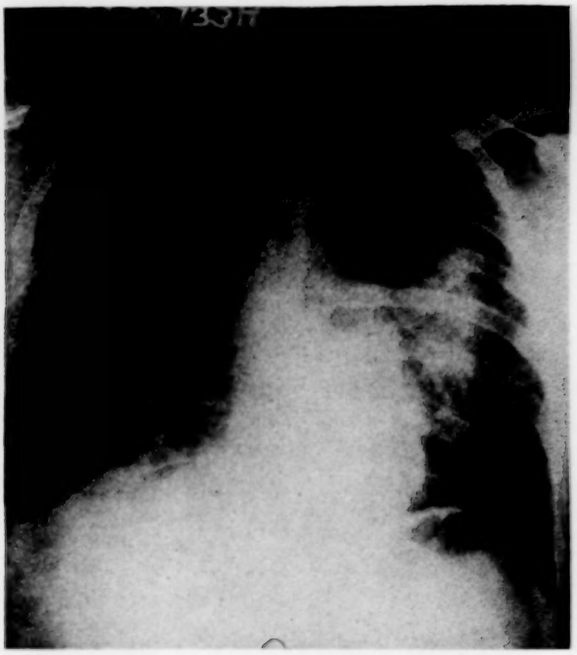

FIG. 5D. X-ray taken at the height of the radiation reaction, Case III.

of the lung showed considerable edematous fluid. The left lung showed similar but less marked changes. The bronchi contained frothy fluid. The remaining organs were not remarkable.

Microscopically, the right ventricular myocardium showed only a rare inflammatory cell underlying the mural thrombus. A tumor nodule was present in the right lung. The only other tumor tissue found was in the form of tumor emboli in the glomerular capillaries. The more peripheral portions of the lungs revealed edema, congestion and patchy areas of interstitial and perivascular fibrosis. In some areas this type of reaction was fairly sharply delimited by interlobular septa from the zones directly under the radiation portals. The lung in these areas showed a more variable histologic picture. The alveolar septa were thickened by intense congestion as well as fibroblastic proliferation. Few inflammatory cells were seen. The alveolar spaces contained fibrin undergoing organization, and in some areas large numbers of unicellular macrophages were present. A few pulmonary venous thrombi were noted, and the perivascular fibrosis was again seen. The bronchi were relatively normal. The changes were interpreted as being due to radiation reaction, with a histologic picture varying from that of fibrotic changes in some areas to those of more "acute" inflammatory reaction in others. (Fig. 6A.)

CASE IV. This twenty-two year old white man noted the development of cough and weight loss while in Service in July, 1954. Examination revealed generalized lymphadenopathy and hepatosplenomegaly. X-ray of the chest demonstrated a large mediastinal mass. A biopsy specimen of the supraclavicular lymph node revealed Hodgkin's granuloma. The patient received nitrogen mustard and cortisone therapy, and in December, 1954, radiation therapy to the neck and mediastinum was started. The patient received a total of 4,477 r to the depth of the mediastinum over a period of fifty-one days, through paired anterior and posterior portals, with slight reduction in size of the mediastinal mass. In March, 1955, he was discharged from Service, and transferred to the Bronx V. A. Hospital (No. 194 647). At this time he was asymptomatic. Radiotherapy to the neck was given in May, 1955, for recurrent nodal enlargement.

In August, 1955, a non-productive cough developed. X-ray of the chest (Fig. 7A) revealed the previously noted mediastinal mass, and nodules in both lung fields believed due to infiltration with Hodgkin's disease. Radiation therapy to the right lung was begun on August 16th, through two upper and lower paired, anterior and posterior 15 by 10 cm. portals, and a total of 1,800 r to the depth of each area of lung was given over a thirty-day period. This was followed by radiation therapy to the left lung through four similarly placed 15 by 13 cm. portals; a total depth dose of 2,000 r to each area was given in thirty days. The pulmonary nodules regressed. (Fig. 7B.) In addition, a pathologic fracture of the left sixth rib in the anterior axillary line was treated at the same time through a tangential portal, delivering 900 r in eight days. During this period evidence of involvement of the cranial nerves by Hodgkin's disease developed, and the patient was readmitted to the hospital for

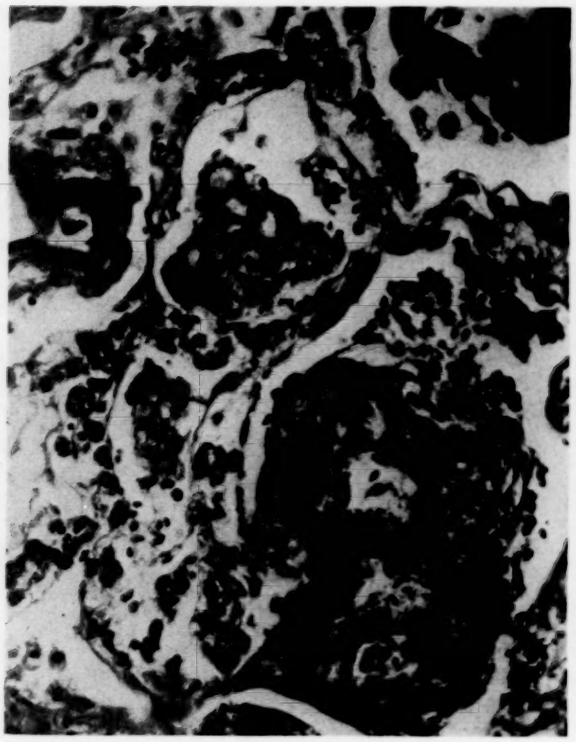

FIG. 6A. Microscopic section from lung of Case III.

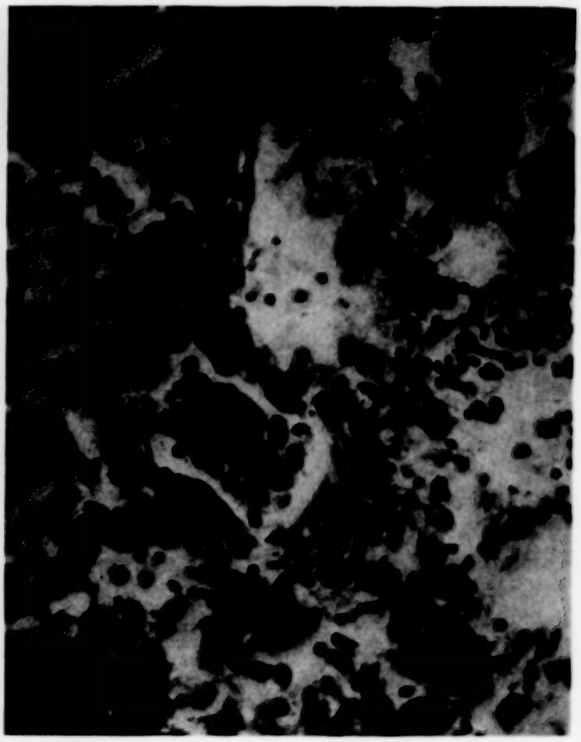

FIG. 6B. Microscopic section from lung of Case IV.

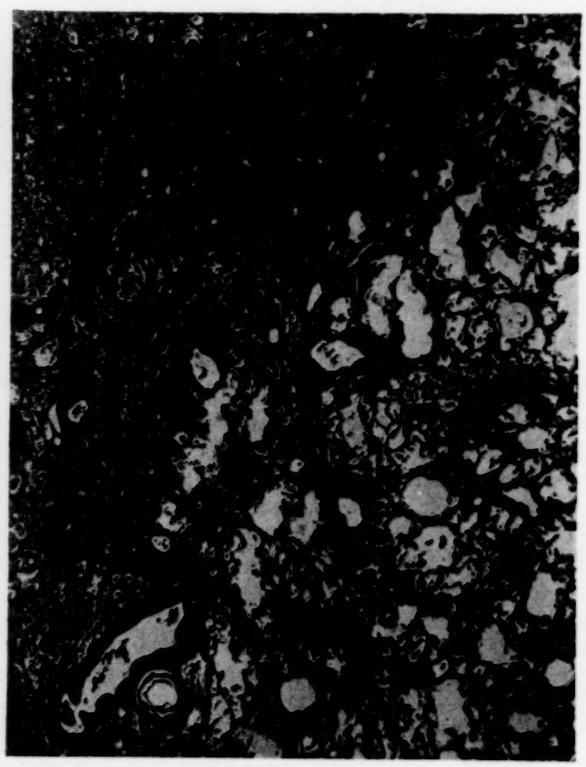

FIG. 6C. Microscopic section from lung of Case V.

additional radiation therapy to the base of the brain.

On October 25th, two weeks after completion of radiation therapy to the left lung and six weeks after completion of radiation therapy to the right lung, an acute cough, dyspnea, cyanosis and tachycardia developed. Examination revealed coarse breath sounds bilaterally. The pulmonic second sound was accentuated. X-ray of the chest (Figs. 7C and 7D) revealed infiltrative changes which were most marked at the right base, and which were interpreted as characteristic of radiation reaction. Laboratory studies were within normal limits except for pulmonary function studies performed one week after the onset of acute symptomatology. (Table II.) The patient was treated with oxygen, antibiotics and digitalis. Prednisone, 30 mg. per day, was begun on October 28th, when a diagnosis of acute radiation reaction was made, and was later increased to 60 mg. Terminally, the temperature rose to 102°F. and the patient died in great respiratory distress on November 13th, two and one-half weeks following the onset of his acute symptoms.

Autopsy was performed six hours after death, following embalming. Both lungs were described as firm on cut section, with a diffuse fine granular appearance. A large mass of matted anterior mediastinal nodes was present, and the superficial and abdominal lymph nodes were replaced by whitish tissue. The parenchymal organs appeared normal.

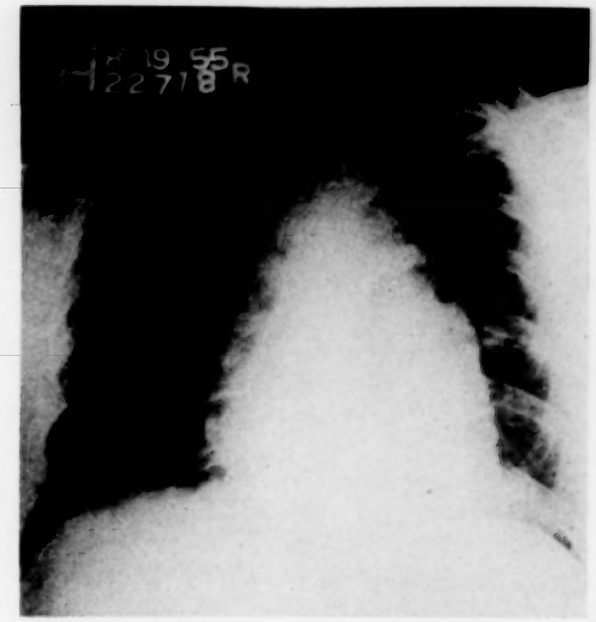

FIG. 7A. X-ray of the chest prior to final courses of radiation therapy, Case IV.

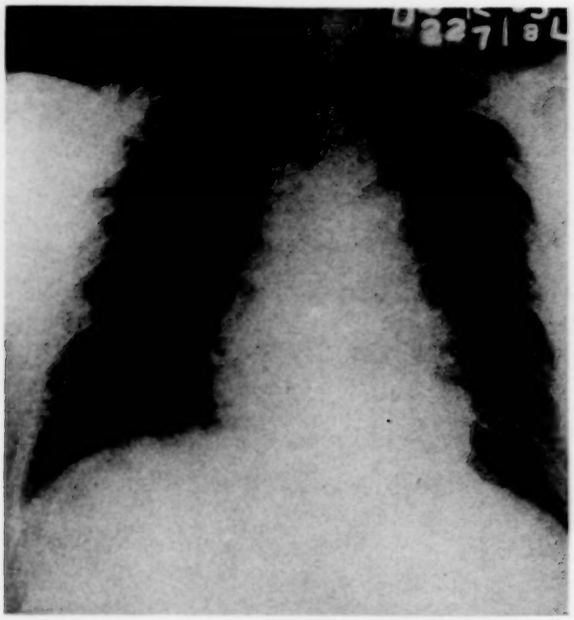

FIG. 7B. X-ray taken at the completion of radiation therapy, Case IV.

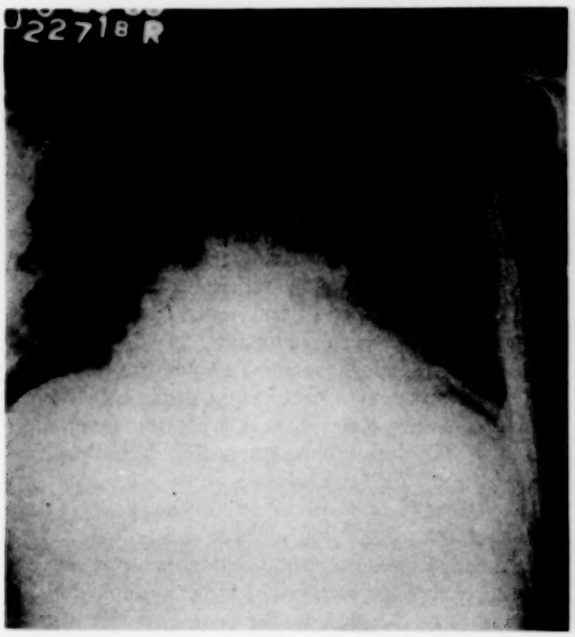

FIG. 7C. X-ray taken two weeks after completion of radiation therapy, Case IV.

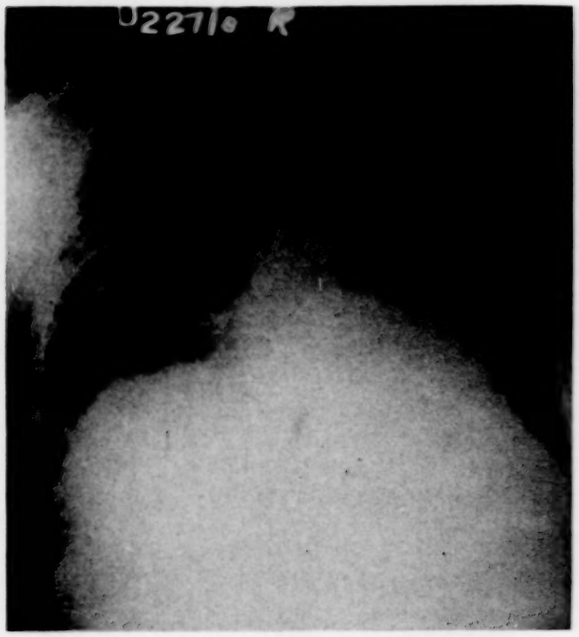

FIG. 7D. X-ray taken shortly before the patient's death, Case IV.

Microscopically, the lymph nodes revealed Hodgkin's disease with extensive fibrotic change, especially in the mediastinal nodes. The liver and spleen were uninvolved. Both lungs revealed moderate edema and congestion. The alveolar septa were diffusely thickened by an interstitial fibrotic process. Large amounts of alveolar exudate, undergoing organization in some areas, were present. Unicellular macrophages were noted in the alveoli. In some areas the alveolar exudate was compressed against the septal walls, giving the appearance of rather characteristic "hyaline membranes." (Fig. 6B.)

The microscopic changes were interpreted as being due to pulmonary radiation reaction.

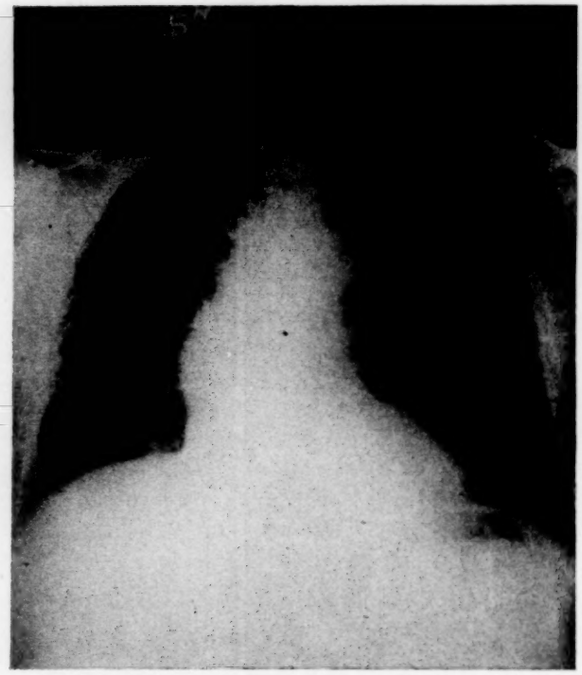

FIG. 8A. X-ray taken prior to final course of radiation therapy, Case v.

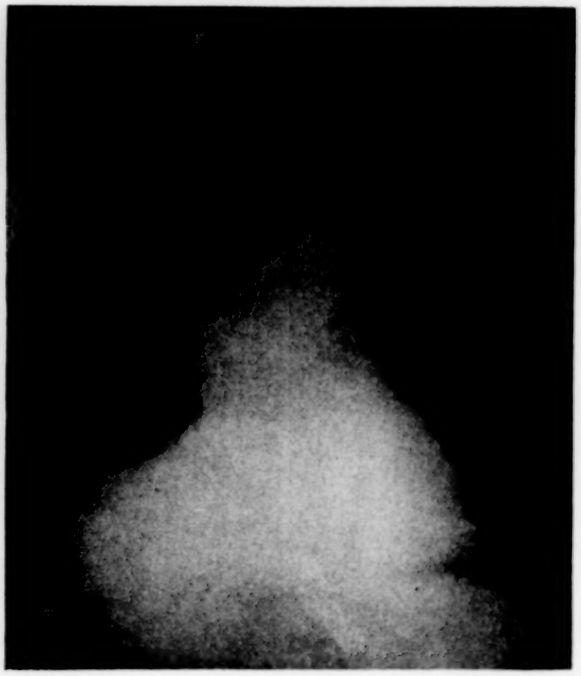

FIG. 8B. X-ray taken at conclusion of radiation therapy, Case v.

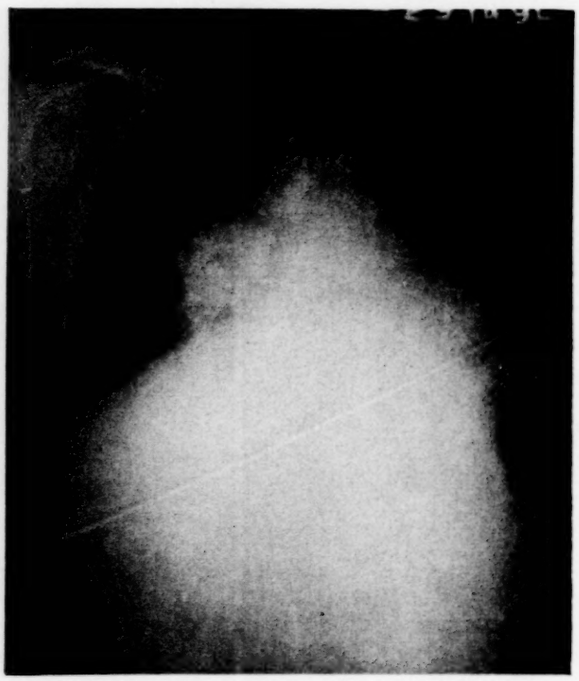

FIG. 8C. X-ray taken six weeks after completion of radiation therapy, Case v.

CASE v. This forty-three year old white man underwent a left orchidectomy in 1952 at another hospital, and a histologic diagnosis of seminoma was made. In 1953 right supraclavicular nodes and superior mediastinal widening were noted. Over a period of twenty-eight days, 2,700 r were given to the mediastinum through four oblique and anteroposterior 10 by 15 cm. portals, with decrease in the size of the mediastinal mass. An infiltrative density developed at the apex of the right lung, presumably due to fibrosis secondary to supraclavicular radiation of 3,500 r. In 1954 a posterior mediastinal mass was noted at the level of the ninth thoracic vertebra and this was treated with 2,700 r to the depth through two lateral and one anterior 8 by 15 cm. portals over a period of forty-one days, with regression of the mass. In January, 1955, a large mass was noted in the region of the posterior segment of the right upper lobe. Over a period of twenty-three days, 3,100 r were given to the depth of this lesion through paired anteroposterior and oblique 7 by 7 cm. portals.

The patient was admitted to the Bronx V. A. Hospital (No. 201 140) in February, 1955, for the treatment of cholelithiasis. Physical examination was normal except for some mild hypertension, and pigmentation of the skin in the region of the previous radiation over the right clavicle. Laboratory studies were within normal limits. X-ray of the chest showed fibrotic changes at the right apex, and an esophagram revealed a mass in the posterior mediastinum. Because of increase in size of this mass, radiation therapy was given in early May, 1955, through paired portals with a dosage of 2,000 r to the depth.

In July, 1955, the patient noted a non-productive cough. Metastatic nodules were seen in the left lung, also changes in the right lung secondary to the previous radiation. (Fig. 8A.) Radiation therapy was given

through two opposing anterior and posterior 13 by 15 cm. portals, so that the left lung received 2,000 r to the depth in twenty-three days. There was apparent relief of cough, and regression of the pulmonary nodules. (Fig. 8B.)

Six weeks after completion of radiation therapy the patient noted increasing dyspnea, fever and cough productive of small amounts of sputum. At this period on physical examination he appeared acutely ill, and was observed to be dyspneic with a respiratory rate of 36, a pulse rate of 140, and a temperature of 101.6°F. Dulness was noted over the left side of the chest, and bronchial breathing and fine rales were heard posteriorly. X-rays of the chest revealed extensive changes compatible with radiation reaction in the left lung, and similar changes on the right, where there was also evidence of tumor. (Fig. 8C.) Electrocardiograms showed a sinus tachycardia; later, non-specific T wave changes were seen. The hemoglobin was 8.1 gm., the red blood count 2,800,000 and the white blood count 10,000. The carbon dioxide content was 17.5 mEq. L. His temperature ranged between 100° and 120°F. during the hospital stay. Shortly after admission 300 cc. of straw-colored fluid was removed from the left chest. The patient was treated intensively with oxygen, antibiotics and bronchodilators, with some decrease in the sputum. Right heart failure developed and the patient was given digitalis. A diagnosis of radiation reaction was made. The patient was too ill for the performance of complete pulmonary function studies but the oxygen saturation of the arterial blood was 76.5 per cent, with a normal carbon dioxide content. Prednisolone, 60 mg. per day, was begun; the dosage was reduced to 40 mg. per day two days later. There was very little change in the clinical course with these methods of therapy except for some improvement in dyspnea. After two weeks of steroid therapy a repeat arterial blood study revealed no significant change in the arterial oxygen saturation. The patient also received small transfusions of packed red cells and two courses of nitrogen mustard. X-rays of the chest showed increase in tumor infiltration on the right. The course continued downhill, and the patient died on December 12th, two months after the onset of symptoms.

At autopsy massive amounts of necrotic tumor were noted in the paratracheal and abdominal lymph nodes, the liver and the peritoneum. The major vessels were atheromatous, and in the left ventricle hypertrophy was present. There were calculi in the gallbladder and the left renal pelvis. Both pleural surfaces were studded with tumor; on the right a large mass of tumor was adherent to the anterior wall of the chest. Small amounts of bilateral pleural fluid were present. Both lungs were firm. On the right a large area of fibrosis fanned outward from the hilum, and similar more extensive changes were present on the left. A few tumor nodules were noted in both lungs.

On microscopic examination the tumor was noted to be extensively necrotic in all areas. A mild degree of nephrosclerosis was present. The other significant findings were limited to the lungs, which contained areas of acute terminal bronchitis and bronchopneumonia. The pleural surfaces were covered with tumor cells. Massive areas of interstitial fibrosis were present, and large numbers of macrophages and some fibrin-like material were seen in the alveolar spaces. Edema fluid was also present, as were rare areas of desquamation and squamous metaplasia of the bronchial epithelium. A striking feature (Fig. 6C) was a sharp line of demarcation, in some zones, between the areas of massive fibrosis and the adjacent less involved lung. Nevertheless, even here patchy areas of involvement quite similar to the changes described directly under the portals were also seen.

These changes were deemed compatible with radiation reaction.

COMMENTS

The lung volume studies in the first patient revealed a normal residual air and markedly reduced vital and total capacities. In addition, it is to be noted that the index of intrapulmonary mixing (alveolar nitrogen remaining after seven minutes of 100 per cent oxygen breathing) is within the normal range. The maximum breathing capacity, while reduced, is performed without spirographic evidence of obstruction. The lung volume changes in Case IV are similar except for a striking reduction in the residual air. These changes are in keeping with those described in cases of marked pulmonary fibrosis.[11]

Ventilatory and gas exchange studies in these two patients reveal the patterns which have been noted in numerous pulmonary diseases which produce impairment of alveolar-capillary oxygen diffusion.[11–13] This is characterized by hyperventilation, reduced oxygen consumption with exercise and elevated dead space measurements with a low arterial pCO_2. Significant alveolar-arterial gradients for oxygen at both levels of oxygenation are present, indicative of increased venous admixture as well as interference with diffusion of oxygen across the pulmonary membrane.

In the second and fifth patient the arterial blood studies do not permit precise definition of the nature of the functional alteration. Nevertheless, in the light of the clinical and pathologic findings it seems reasonable to attribute the arterial blood anoxia (low pO_2 and arterial oxygen saturation), in the presence of effective alveolar ventilation (normal or low arterial

pCO_2), to impairment of diffusion of oxygen across the pulmonary membrane. In any event the clinical picture in all five patients was so striking and characteristic that at the bedside the nature of the pulmonary functional abnormalities could be surmised.[12]

DISCUSSION

The incidence of radiation pneumonitis,[1–3] and the factors leading to its development, are in doubt. Most radiologists suggest that the appearance of radiation fibrosis depends, at least in part, upon the amount of radiation given and the volume of tissue exposed,[6,14,15] although other factors such as age, infection and the presence of neoplastic disease or pulmonary emphysema may influence the pathologic alterations.[1,16] All of these factors may be of some importance in determining why in one patient and not another serious pulmonary radiation reaction develops but it would seem clear from our own observations that the total dose of radiation delivered to both lungs (during one or more courses of radiation therapy) and the brevity of the period in which a significant volume of lung tissue is radiated are probably significant, if they are not indeed the two most important single factors. For example, in Cases I and III the fatal syndrome occurred after 4,100 and 3,200 r, respectively, were given in a relatively short period. This contrasts with Case II in which a much larger dose 6,000 r was given over a period of forty days before pulmonary fibrosis occurred. It does not seem unreasonable, therefore, to relate the individual development of pulmonary fibrosis to the volume of lung exposed, the total depth radiation and, finally, the rapidity with which this total depth radiation is given. It is suggested also that cumulative effects of radiation may occur. One can speculate, for example, that in Cases IV and V the previous courses of radiation produced some pathologic changes in the lung, without clinical manifestations, because it was only after multiple courses of therapy that the clinical picture of radiation reaction developed.

Warren and Spencer[3] believe that the damage begins with injury to the alveolar cells and capillary endothelium with resultant edema, swelling, necrosis and then proliferation of alveolar epithelium and capillary endothelium. As a result of connective tissue damage, fibroblastic proliferation occurs, especially in the alveolar wall. These authors noted that the acute reaction was characterized by deposition of a hyaline-like material in the alveoli which occasionally was continuous with the alveolar wall. Others believe this to be a non-specific finding.[17] The late reaction was thought to be characterized by a vascular hyaline fibrosis with thickening of alveolar walls and septa. Peribronchial and perivascular fibrosis[1] as well as disruption of the elastica[18] have been reported. Nearly all cases studied revealed evidence of organizing pneumonia, and some showed emphysematous changes and varying degrees of bronchial and pulmonary infection. It is noteworthy, however, that the pathologic findings in four of our five cases reported herein reveal little or no evidence of infection.

The clinical picture as previously reported in cases of radiation pneumonitis and fibrosis of the lung is so variable that a typical syndrome cannot be precisely defined. For example, it is common experience that many patients in whom localized pulmonary fibrosis develops after radiation for mammary carcinoma are asymptomatic.[1] Mild dyspnea and productive cough is frequently seen in symptomatic patients.[1] With time, these may regress.[1] In a small percentage of patients a clinical picture characterized by fever and severe progressive pulmonary insufficiency develops, frequently leading to cor pulmonale and death in cardiac failure.[6] It is to be noted that these fatal cases with severe symptomatology show extensive pulmonary parenchymal changes which are almost invariably bilateral.

Although complete pulmonary function studies are not available in any reported series, the lung volume studies in isolated cases of radiation, pneumonitis and fibrosis of the lung are characteristic of severe degrees of pulmonary fibrosis.[11] Arterial oxygen unsaturation at rest[11] and with exercise[7] together with pulmonary hypertension on exercise[7] have been reported.

It seems reasonable in the patients discussed here to relate the acute onset of symptomatology to the effects of radiation. Furthermore, it will be noted that the changes on x-ray suggestive of pulmonary fibrosis correspond quite well to the portal areas of radiation. Both lungs of necessity were involved in all patients, either because of bilateral radiation or by the use of lateral or oblique multidirectional portals. The microscopic sections from all areas of the lung show the same type of extensive changes and make it quite likely that these changes are radiation-

induced and not significantly related to the primary disease which these patients had. In view of the severe degree of organizing pneumonia, obliteration of alveoli and thickening of alveolar walls, it is not surprising that severe impairment of gas exchange was present in these patients. This is quite analogous to the numerous cases of other types of interstitial fibrosis with similar functional pictures and pathologic findings reported by previous authors.[11–13] The clinical picture in this advanced severe degree of radiation reaction in the lung reflects not only the apparent functional difficulties but also the severe inflammatory changes resulting from lung injury. The acute febrile nature of the illness in part reflects these inflammatory changes. In four of the five cases onset of the acute syndrome followed closely the cessation of radiation therapy. The reason for the delay in onset of symptoms in Case III must remain speculative at the present time. Finally, it is our considered opinion that such radiation reactions were uncommon in the past because available technic then did not permit as extensive depth radiation as present-day technics do.

Cosgriff and Kligerman[19] have reported striking temporary symptomatic improvement with the use of steroids in a patient with acute radiation pneumonitis. Steroid therapy of various pulmonary granulomatoses has been reported to improve pulmonary function as well as general symptomatology.[13,20–22] There is a real question in follow-up studies as to how much objective and permanent improvement occurs with such therapy, and how much is subjective. Cortisone therapy of sarcoid may accelerate the development of pulmonary fibrosis and patients with pre-existing fibroses are probably not benefited.[13,20] In the patients reported herein there was no lasting objective response to steroid therapy. Friedenberg et al. have suggested the use of cortisone in the prophylaxis of radiation pneumonitis.[15] A long-term, controlled study would be of value in assessing this point.

SUMMARY

1. Five patients with radiation pneumonitis and fibrosis leading to severe pulmonary insufficiency are presented. Correlated clinical, functional and pathologic findings indicated that impaired diffusion across the alveolar-capillary membrane played an important role in the functional abnormality in each instance.

2. Steroid therapy, utilized in four patients, failed to alter the course of the acute syndrome.

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ADDENDUM

Since this paper was prepared Dr. Nickson and his group at Memorial Hospital have reported upon the effects of steroid therapy in preventing or ameliorating radiation fibrosis in patients who received radiation to the lungs for cancer. Their experiences in some fifteen cases indicated no remarkable alteration of the clinical course with steroids nor did they prevent the appearance of fibrosis when used prophylactically.[23]

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Renal Insufficiency and Hypertension Associated with Secondary Amyloidosis*

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REPORTS on the frequency with which renal insufficiency and hypertension complicate secondary amyloidosis show great variations. Fishberg[1] states that "renal insufficiency with consequent nitrogen retention and uremia occurs in unusual instances of the amyloid contracted kidney." However, he further indicates that such cases may not be so rare as is generally thought because patients who have renal involvement in amyloidosis are not studied intensively. Gutman[2] states that "in exceptional instances, obliteration of nephrons may be extensive enough to cause uremia." In a review of twenty-eight cases of secondary amyloidosis with renal involvement, Dahlin[3] found three cases of azotemia, one with hypertension. He described other cases of nitrogen retention but these were extrarenal in origin. Rosenblatt[4] found one instance of nitrogen retention but none of hypertension in fifteen cases of amyloidosis of the kidney.

In contrast to these findings are those of Mark and Mosenthal,[5] Auerbach and Stemmerman,[6] Theilum and Lindahl,[7] Dixon,[8] Altnow, Van Winkle and Cohen,[9] Jacobi and Grayzel.[10] These investigators found a much higher incidence of renal insufficiency and hypertension in their patients. Bell[11] suggests that renal insufficiency and hypertension can be correlated with amyloid involvement of the kidney. Numerous reports have been made of single cases, or small series of cases, of renal failure with or without hypertension.[12–16] Table 1 summarizes the findings in a large series of cases.

This report concerns thirty-nine cases of secondary amyloidosis gathered from the postmortem records of the Goldwater Memorial Hospital, Welfare Island, New York and the Maimonides Hospital of Brooklyn. Many of these patients were also observed clinically by us prior to death. All were cases of so-called secondary amyloidosis. Several cases of atypical or primary amyloidosis were omitted from the series, although the problem of renal failure and hypertension in primary amyloidosis may well be the same as that in secondary amyloidosis.[3,15] None of these patients had contracted kidneys at postmortem examination and only one of all the cases listed in Table 1 showed contracted kidneys.

TABLE 1
INCIDENCE OF RENAL INSUFFICIENCY AND HYPERTENSION IN CASES OF AMYLOIDOSIS

Author	No. of Cases	Patients with Renal Insufficiency	Patients with Hypertension
Mark & Mosenthal[5]	67	20	1
Auerbach & Stemmerman[6]	162	64	4 per cent
Theilum & Lindahl[7]	17	7	Not given
Dixon[8]	46	12	4 of 35
Altnow et al.[9]	29	9	35 per cent
Rosenblatt[4]	15	1	0
Jacobi & Grayzel[10]	12	3	Not given
Present series	39	22	8

The clinical diagnosis of amyloidosis in our series was established in only a few patients by the Congo red absorption test; most of the group absorbed less than 90 per cent of injected dye. When hypertension and renal insufficiency were present and when the Congo red test gave normal results, the usual diagnosis was chronic glomerulonephritis. In those patients with proved amyloidosis the presence of renal insufficiency and hypertension was ascribed to some disease of the kidney other than amyloid involvement.

To illustrate the difficulty in determining the diagnosis of renal amyloidosis antemortem,

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TABLE II

OBSERVATIONS IN THIRTY-NINE CASES OF SECONDARY AMYLOIDOSIS

Patient	Age and Sex	Primary Diagnosis and Duration (yr.)	Blood Pressure (mm. Hg)	Urine		Blood Urea Nitrogen (mg. %)	Organs Involved (postmortem)
				Specific Gravity*	Proteinuria†		
C. A.	44,M	Tuberculosis, 10	200/120	Low	Heavy	40–137	Kidney, liver, spleen, adrenal
I. S.	50,M	Empyema, 15	190–210/100–110	Low	Heavy	110–160	Kidney, liver, spleen, adrenal
A. E.	51,M	Bronchiectasis, 8	120–170/94–100	Moderate	Heavy	11–38	Liver, kidney, spleen, thyroid
C. N.	54,M	Central nervous system lues, 35	160–230/95–120	Low	Heavy	16–38	Liver, kidney, spleen
G. U.	60,F	Rheumatoid arthritis, 5	190/100	Moderate	Heavy	108–184	Kidney, liver, spleen, thyroid
A. K.	72,F	Tuberculosis, 42	180–192/80–104	Low	Heavy	33–36	Kidney
A. H.	74,M	Bronchitis, 3	140–180/95–110	Moderate	Heavy	18–94	Kidney, liver, spleen
S. C.	76,M	Rheumatoid arthritis, 5	170/105	Moderate	Mild	23–41	Kidney, liver, spleen
A. O.	24,F	Tuberculosis, 6	90–105/60–75	Moderate	Heavy	25–46	Kidney, liver, spleen
J. S.	33,M	Chorionepithelioma; rheumatoid arthritis, 7	130–145/85–95	Low	Heavy	17–44	Kidney, liver, spleen
M. B.	40,M	Rheumatoid arthritis, 17	110–190/30–65	Moderate	Mild	15–97	Kidney, liver, spleen, adrenal
S. A.	40,M	Rheumatoid arthritis, 7	110–120/60–80	Low	Heavy	5–119	Kidney, liver, spleen, adrenal
J. M.	43,M	Rheumatoid arthritis, 9; tuberculosis, 10	120–140/70–95	Moderate	Heavy	11–16	Kidney, liver, spleen, adrenal
E. J.	46,M	Hodgkin's disease, 5	108/78	High	Heavy	11	Kidney, spleen, adrenal
J. M.	51,M	Bronchiectasis, 1½	95/60	Moderate	Heavy	69–122	Kidney, liver, spleen, adrenal
F. W.	53,F	Pseudomyxoma ovary, 11	110/70	Low	Moderate	16–156	Kidney, liver, spleen
G. G.	53,M	Rheumatoid arthritis, 14	100–160/60–80	High	Heavy	9–140	Kidney, liver, spleen, adrenal
B. C.	54,M	Rheumatoid arthritis, 8	120–140/70–90	Moderate	Moderate	13–157	Kidney, spleen, thyroid
I. G.	57,F	Bronchitis, 4	125/70	Moderate	Moderate	11–30	Kidney, liver, spleen, adrenal

TABLE II (*Continued*)

Patient	Age and Sex	Primary Diagnosis and Duration (yr.)	Blood Pressure (mm. Hg)	Urine		Blood Urea Nitrogen (mg. %)	Organs Involved (postmortem)
				Specific Gravity*	Proteinuria†		
S. G.	62,F	Varicose ulcer, 2; lymphoma, duration not known	140–170 / 80–90	Low	Moderate	56–97	Kidney, liver, spleen
A. C.	63,M	Rheumatoid arthritis, 5	120–150 / 65–90	Moderate	Heavy	12–127	Kidney, liver, spleen
M. W.	65,M	Rheumatoid arthritis, 16	120–170 / 60–80	Moderate	Heavy	14–95	Kidney, liver, spleen, adrenal
B. D.	67,M	Rheumatoid arthritis, 21	110–115 / 70–80	Moderate	Mild	18–40	Kidney, liver, spleen
D. C.	68,M	Tuberculosis, 2 months	140 / 70	High	Heavy	28	Kidney, spleen
A. S.	74,F	Bronchiectasis, 7	100 / 70	Low	Heavy	10–12	Kidney, spleen
J. F.	27,M	Hodgkin's disease, 1	106 / 60	High	None	8–19	Kidney, liver, spleen
R. M.	28,M	Tuberculosis, bronchiectasis, 5	100 / 60	High	Negative	7	Kidney, spleen
R. M.	33,M	Rheumatoid arthritis, 11	110–135 / 50–70	Moderate	Negative	6–16	Kidney, liver, spleen
P. A.	35,M	Multiple sclerosis, 14	110 / 70	Moderate	Mild	8–15	Kidney
T. N.	40,M	Tuberculosis, rheumatoid arthritis, 12	110–120 / 70–80	High	Moderate	10–16	Spleen
O. B.	41,M	Bronchiectasis, 7	110–120 / 60–70	Low	Negative	10–15	Kidney, liver, spleen
H. B.	43,M	Rheumatoid arthritis, 2; ulcerative colitis, 4	120 / 80	Low	Negative	4	Kidney, liver, spleen
A. E.	50,M	Rheumatoid arthritis, 17	120–140 / 80	Moderate	Negative	6–17	Kidney, liver, spleen
F. S.	56,F	Tuberculosis of kidney and bone, 3	115 / 80	Moderate	Mild	8–18	Kidney, spleen
E. M.	58,F	Actinomycosis, 4	115 / 75	Low	Mild	5–7	Kidney, liver, spleen
M. P.	63,M	Emphysema, duration not known	126 / 90	Moderate	Moderate	11–12	Kidney, liver, spleen
J. C.	64,M	Bronchogenic carcinoma, duration not known	120 / 70	Moderate	Mild	20	Kidney, liver, spleen
J. D.	66,M	Tuberculosis, 4; rheumatoid arthritis, 4	118 / 66	Low	Negative	13–22	Kidney, liver, spleen, adrenal
E. S.	68,F	Bronchiectasis, 2	100 / 55	Moderate	Moderate	17-22	Kidney, liver, spleen

* Low = 1.006 to 1.011; moderate = 1.012 to 1.019; high = 1.020 or over.
† Mild = trace—1 plus; moderate = 2 plus; heavy = 3 plus to 4 plus.

two cases are cited. These cases suggest that whenever a disease exists which may lead to secondary amyloidosis the finding of proteinuria implies amyloidosis of the kidney and this diagnosis is not excluded by the presence of hypertension and renal insufficiency.

CASE REPORTS

CASE I. C. A., a forty-four year old man, was admitted to the Maimonides Hospital in January 1953. He had had pulmonary tuberculosis for ten years. In 1943 pneumothorax was instituted and in 1945 a thoracotomy was performed, which resulted in a draining sinus. In November 1952, he was admitted to another hospital for bleeding from the rectum and from the thoracic sinus tract. No hematologic abnormality was discovered. The urine at this time was of low specific gravity (1.008) and contained 3 plus proteinuria. No chemical examinations of the blood were recorded. The patient was transferred to the Maimonides Hospital for closure of the draining sinus.

On admission the liver was felt two inches below the costal margin. Amyloidosis was suspected but a Congo red test showed only 74 per cent retention of the dye. A gingival biopsy specimen did not reveal amyloidosis. Blood urea nitrogen on admission was 40 mg. per cent. Urine examinations showed 2 to 4 plus proteinuria, specific gravity of 1.004 to 1.008, and many hyaline and granular casts. Blood pressure was consistently 195 to 210/100 to 110 mm. Hg. Hematologic study revealed normocytic normochromic anemia and thrombopenia.

The patient's course was progressively downhill. He bled frequently from the genitourinary and gastrointestinal tracts, from the gum biopsy site and the sinus tract. Blood urea nitrogen rose progressively to 137 mg. per cent. Shortly before death the patient complained of severe headache, and convulsions and a comatose state ensued.

While amyloidosis was suspected clinically, most observers felt that the lesion of the kidney was chronic glomerulonephritis because of the severe hypertension and marked renal insufficiency. However, postmortem examination revealed amyloidosis of the liver, spleen, kidney and adrenal gland. Left cerebellar hemorrhage, caseous and fibrotic tuberculosis of the right lung and hilar glands, and a draining thoracic sinus were noted.

CASE II. I. S., a fifty year old man, was first admitted to the Maimonides Hospital on December 24, 1952, complaining chiefly of shortness of breath and swelling of the feet and abdomen of three weeks' duration.

The history revealed that in November 1938 right-sided empyema developed for which thoracotomy was performed. The empyema cavity persisted and in April 1939 thoracotomy was repeated. At this time the blood pressure was 104/60 mm. Hg, the urine specific gravity 1.005 to 1.020 with 3 to 4 + proteinuria. Blood urea nitrogen was 19.4 mg. per cent. Secondary amyloidosis was suspected but a Congo red test showed only 60 per cent retention of the dye. After the patient's release from the hospital purulent material continued to drain from the wound site. However, he felt well and was able to work. In 1947 a respiratory infection developed and drainage from the thoracotomy wound became profuse. On readmission to the hospital an encapsulated empyema was found for which catheter drainage was instituted. Urinalysis showed 4 plus proteinuria. Blood urea nitrogen was 19.7 mg. per cent. He was released after several days, returned to work and felt reasonably well until three weeks prior to admission to the Maimonides Hospital.

Physical examination revealed an acutely ill man with generalized anasarca. The temperature was normal, the pulse rate was 92, the blood pressure 190/110. Fresh hemorrhages were noted in the fundi. Wheezes and rales were present throughout both lung fields and fluid was present in the right chest. The heart was enlarged. The liver and spleen were easily felt. The specific gravity of the urine ranged from 1.002 to 1.012, proteinuria from 2 to 4 plus. A few red and white blood cells were seen. The serum cholesterol was 316 mg. per cent, albumin 2.3 gm. per cent and globulin 3.7 gm. per cent. Only 50 per cent retention of Congo red was noted. Hemoglobin was 8 gm., the red blood count was 2.7 million and the blood urea nitrogen 131 mg. per cent.

On salt restriction, bedrest and transfusion, the patient improved and was discharged. He was readmitted on February 13, 1953 because of nausea and vomiting. Physical examination revealed no changes. Blood urea nitrogen rose to 140 mg. per cent. Symptoms of uremia progressed rapidly, with convulsions, and the patient died on April 19, 1953. The clinical impression was that the patient had chronic empyema and chronic glomerulonephritis. Most observers believed it unlikely that amyloidosis would have been present for fifteen years and, furthermore, that uremia and hypertension are more characteristic of chronic glomerulonephritis. However, autopsy, which was limited to the abdominal viscera, revealed amyloidosis of the liver, spleen, kidneys and adrenals.

Table II presents pertinent data on our thirty-nine cases.

Analysis of Table II reveals the following facts. Of the thirty-nine patients, thirteen died in uremia. Four of these thirteen had hypertension. Nine other patients had significant nitrogen retention (urea nitrogen 25 to 50 mg. per cent), and four of these also had hypertension. Nine patients died in uremia without hypertension. All the patients who died in uremia or exhibited nitrogen retention also had moderate to heavy proteinuria. The specific gravity of the urine was variable.

Postmortem findings showed no correlation between hypertension and the presence or absence of adrenal amyloidosis. No instances of contracted kidney occurred in this series. None of the patients had Addison's disease.

The duration of the amyloidosis is difficult to estimate. In most of our cases it was at least of several years' duration. In one case amyloidosis was known to have existed for fifteen years and in another for several months. Both died in uremia.

CONCLUSIONS

1. Renal insufficiency and hypertension occur frequently in secondary amyloidosis.
2. The clinical course in amyloidosis of the kidney frequently resembles that of chronic glomerulonephritis.
3. The debilitating effect of the primary disease in secondary amyloidosis does not seem to prevent development of hypertension.
4. No correlation can be found between the presence or absence of hypertension and amyloidosis of the adrenal gland.
5. Whenever secondary amyloidosis is suspected, the presence of proteinuria should suggest amyloid involvement of the kidney since this is the earliest and most consistent finding in amyloidosis of the kidney.

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Oral Phenylbutazone in the Treatment of Acute Gouty Arthritis*

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The beneficial action of phenylbutazone in acute gouty arthritis has been noted in many early clinical trials in various rheumatologic disorders.[8,12,13,16] Further studies have confirmed and extended these initial observations and indicate that this synthetic pyrazolone derivative is particularly effective in controlling symptoms of acute gouty attacks.[1,3,4,6,9,10,11] Table 1 summarizes reports from the American literature in which the clinical response of acute gout to phenylbutazone could be evaluated. In those cases treated within the first week of the acute attack, phenylbutazone relieved 82 per cent of the 315 reported attacks. Kuzell,[1] Steinbrocker[4] and Gutman[3] have commented on the early subjective pain relief which precedes objective resolution of the other signs of joint inflammation. Our observations indicate that this early control of pain is a constant and significant advantage of phenylbutazone and may be obtained earliest with relatively large initial drug doses. Determinations of serum phenylbutazone level and serum urate concentration made at the time of clinical pain relief indicate that the drug's effectiveness in relieving the pain of acute gout is related to the attainment of a relatively low but constant serum drug level and is unrelated to its uricosuric effect.

This presentation describes our experiences in treating sixty consecutively observed acute attacks of gout with various doses of phenylbutazone administered orally.

MATERIAL AND METHODS

Sixty acute attacks of gout occurring in forty-two consecutive admissions of male patients with gouty arthritis have been treated with oral phenylbutazone. All cases were under observation by one or more of the authors either in the Veterans Administration Hospital, Denver, Colorado, or the Arthritis Clinic of Colorado General Hospital. The diagnosis was established by the criteria previously described by two of us.[9] In fourteen patients the disease was in a chronic stage with superimposed bouts of acute joint inflammation (stage III); the remaining twenty-eight patients suffered acute attacks but had symptomless intercritical periods (stage II).

Phenylbutazone was administered orally as 100 or 200 mg. coated tablets. For the most part, the dosage schedules used were 100 mg. every four hours (400 to 600 mg./day), 200 mg. every four hours (800 to 1,200 mg./day) and 400 or 800 mg. as a single dose. If the early clinical improvement was not maintained, these single doses were often supplemented after eighteen or twenty-four hours. The period of drug administration ranged from one to five days.

Therapeutic response was evaluated by two criteria: the time required to produce significant pain relief estimated at 50 per cent or more, and the time required to resolve evidences of joint inflammation. The first criterion, which is both subjective and objective, was defined arbitrarily as a definite subjective relief of pain, with restoration of comfortable function of the involved joints. Phenylbutazone blood levels were determined by the heptane extraction method of Burns et al.[14] Serum urate concentrations were determined colorimetrically using Archibald's modifications of the Kern and Stransky method as described by Forsham.[15]

RESULTS

The acute attack of gout responded to oral phenylbutazone in two phases. First, marked relief of joint pain occurred with minimal or no objective changes in the other signs of inflammation. Second, the remaining signs of joint inflammation gradually resolved. The initial pain reduction occurred within twenty-four hours in fifty-five attacks, and the subsequent resolution of joint inflammation occurred within seventy-two hours in forty-six attacks.

The relationship of the dosage schedule to the

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TABLE I

PHENYLBUTAZONE THERAPY OF GOUT: REVIEW FROM LITERATURE

Author	No. of Patients	No. of Attacks	Dose	Response	
				Less than One Week	Greater than One Week
Kuzell et al.[1]	200	200	200 to 1,600 mg./day by mouth or 1 gm. intramuscularly or intravenously	168	32
Kidd et al.[2]	16*	40	400 to 800 mg./day by mouth; 400 to 1,000 mg. intramuscularly	30	10
Gutman and Yü[3]	16	20	400 to 800 mg./day by mouth	13	7
Steinbrocker et al.[4]	14	16	400 to 800 mg./day by mouth; 600 to 1,000 mg. intramuscularly	13	3
MacKnight[5]	11†	11	200 to 600 mg./day by mouth	10	1
Johnson et al.[6]	10	20	200 to 600 mg./day by mouth	16	4
Byron and Orenstein[7]	8	8	400 to 800 mg./day by mouth	7	1

* Four patients received irgapyrin.[8]
† All cases of tophaceous gout.

TABLE II

RELATIONSHIP OF PHENYLBUTAZONE DOSAGE TO TIME OF PAIN RELIEF

(Cumulative Data)

Dosage (mg.)	No. of Attacks	Hours				
		4	8	12	16	24
100 q. 4 h.	22	2	12	18	21	22
200 q. 4 h.	17	1	6	16	17	..
400 stat.	12	10	11	11	11	12
800 stat.	7	6	6	6	7	..

TABLE III

RELATIONSHIP OF PHENYLBUTAZONE DOSAGE TO TIME OF RESOLUTION

Dosage (mg.)	No. of Attacks	Hours			
		24	48	72	72
100 q. 4 h.	18	10	14	17	18 (80)
200 q. 4 h.	14	6	9	13	14 (150)
400 stat.	7	4	6	7	7
400 stat. + ID	5	2	2	4	5 (84)
800 stat.	4	2	4	4	4
800 stat. + ID	3	1	2	2	3 (120)

promptness of the initial phase (pain relief) is shown in Table II. This effect occurred earliest with the large single initial phenylbutazone doses of 400 to 800 mg. In sixteen of nineteen attacks it occurred in four hours. In five of the patients treated with 800 mg. the pain in the involved joints was relieved within two hours.

When a dose of 100 mg. every four hours was administered, pain relief occurred within twelve hours in eighteen of twenty-two attacks, and within eight hours twelve of these attacks had aborted. In only two attacks was pain relief afforded by four hours. All patients were relieved of joint symptoms by twenty-four hours. On a dose of 200 mg. every four hours all of seventeen attacks were relieved of pain in sixteen hours while in only one instance did this happen in four hours.

The relationship of dosage to resolution of joint inflammation is shown in Table III. On a dosage of 100 mg. every four hours ten of eighteen attacks showed resolution of all signs of inflammation in twenty-four hours. Seventeen of eighteen attacks were resolved within seventy-two hours. On a dosage schedule of 200 mg. every four hours six of fourteen attacks showed resolution in twenty-four hours. In thirteen of fourteen attacks resolution occurred within seventy-two hours. On a dose of 400 mg. resolution occurred within twenty-four hours in five of ten attacks. Resolution was complete in seventy-two hours in nine of these. With a dose of 800 mg.

resolution of the attack occurred within twenty-four hours in three patients, three patients resolved their attacks in forty-eight hours, and another in 120 hours. Although a single large initial dose of phenylbutazone (400 to 800 mg.) effects early pain relief, eight of nineteen acute attacks so treated required institution of an intermittent dosage schedule to maintain the initial improvement and effect final resolution.

TABLE IV
SERUM PHENYLBUTAZONE LEVEL AT TIME OF PAIN RELIEF

Patient	Dosage (mg.)	Time (hr.)	Serum Phenylbutazone (mg. %)
1	100 q. 4 h.	10	2.48
2		8	2.92
3		8	3.10
4	200 q. 4 h.	7½	6.08*
5		7	3.40
6	400 stat.	6	3.68
7		4	2.76
8		4	3.92
9		4	3.72
10		3	3.24
11	800 stat.	3	2.66
12		2	2.10

* Not included in final data as value is improbable at the 1% level of confidence. Mean drug level 3.09 ± 0.57.

Serum Drug Level at Time of Relief of Pain. Table IV shows the serum phenylbutazone levels in twelve different patients at the time when pain relief was effected when the various dosage schedules were employed. It is apparent that the serum drug level at this time varied within narrow limits, from 2.1 to 3.9 in eleven of twelve instances. Further, the time required to attain this effective serum drug range was inversely proportional to the magnitude of the initial drug dose. The mean serum drug level at the time of pain relief was 3.09 mg. per cent, with a standard deviation of ±0.57. In those instances in which serum urate concentration was studied, no significant change was noted.

Since there is a relationship between the magnitude of the initial drug dose and the time of attaining an effective serum phenylbutazone level, drug levels were determined in gouty and non-gouty subjects at two, four, eight and twelve hours on varying dosage schedules. None of these subjects was being treated for joint symptoms at the time this series of observations was being made. The larger doses (800 mg. and 400 mg.) produced a more rapid rise in the serum drug concentration than the smaller doses (200 mg. and 100 mg.). However, there was considerable variation in the serum drug level for any given dose, particularly in samples obtained before eight hours. Nevertheless, the time of attainment of a serum phenylbutazone level sufficient to relieve pain correlated with the time of pain relief observed clinically for the various doses. At two hours, over half of the subjects receiving an 800 mg. initial dose had attained a serum drug level within the pain relieving zone. By four hours, all subjects receiving 800 mg. had serum levels above the observed pain relief zone. It is of interest to consider the result of this experiment in relationship to the clinical observations in the sixty acute attacks which form the basis of this report. It was observed that five of seven attacks treated with 800 mg. aborted within two hours; six of seven by four hours. With a single 400 mg. dose, nine of ten subjects had serum phenylbutazone levels by four hours within or exceeding the pain relief zone. Clinically, ten of twelve attacks treated with 400 mg. of phenylbutazone obtained pain relief by four hours. With intermittent administration of 200 mg. every four hours an effective serum phenylbutazone level resulted in eight of ten instances within eight hours. Clinically, six attacks treated with this dose responded by eight hours, and sixteen of seventeen by twelve hours. Intermittent administration of 100 mg. every four hours resulted in over half of the patients attaining an effective serum level by the end of eight hours, and all patients had a serum level in the pain relief zone by the end of twelve hours. Clinically, twelve of twenty-two attacks treated with 100 mg. every four hours responded in eight hours, and eighteen of twenty-two by twelve hours.

The wide individual variation of serum phenylbutazone levels, some of which fall outside of the zone of effective pain relief, may explain some of the variation in response observed clinically.

DISCUSSION

In view of the availability of several proved agents for the therapy of acute gout, the use of any new agent requires justification: (1) It should be easily administered and thera-

peutically effective in the great majority of cases; (2) it should effect earlier relief of pain; (3) it should be less noxious or toxic than currently used agents and (4) it should have some special effects, such as therapeutic efficiency late in the course of an acute attack of gout.

In our hands, treating mainly hospitalized bed patients, oral administration of phenylbutazone has controlled pain in fifty-six of fifty-eight attacks of acute gout within twenty-four hours, and has resolved all evidence of the disease within seventy-two hours in forty-seven of fifty-one attacks. Improvement with oral colchicine seldom occurs before eight to twelve hours. Pain relief is obtained with oral phenylbutazone as early as two to four hours following administration of a large initial dose. In sixteen of nineteen attacks significant pain relief occurred within four hours when initial doses of 400 or 800 mg. were given.

Moreover, the noxious side effects (diarrhea, nausea and vomiting) which occur so commonly with the dose of colchicine required to effect pain relief were not a problem with phenylbutazone. Occasionally a patient who received 800 mg. doses complained of mild epigastric burning. One patient, a seventy-eight year old patient with diabetes who was later discovered to have an incomplete bowel obstruction, vomited a 400 mg. dose. The following day he received 100 mg. every four hours for seventy-two hours and responded favorably without further toxicity. In another, an extremely tense and anxious young man whose attack of gout had responded within seventy-two hours to a single 800 mg. dose, tarry stools and epigastric distress developed eight days after treatment. The temporal relationship of the single dose of medication to the onset of the gastrointestinal dysfunction strongly suggests that they are unrelated in this case. Otherwise, no undesirable side reactions attributable to phenylbutazone have been observed during or after the three to four days of therapy necessary for treatment of the acute attack of gout.

Well established attacks of acute gout have been noted to respond to phenylbutazone. Moreover, both the chronic and the intermittent stages of the disease responded favorably. In our experience, in no other form of arthritis has the response to phenylbutazone therapy been so dramatic as in acute gouty arthritis. Indeed, this latter property may serve as a useful diagnostic test agent for acute gout.

CONCLUSION

1. The effect of various dosages of orally administered phenylbutazone has been studied in sixty acute attacks of gout.

2. The response of acute gouty arthritis to phenylbutazone is dramatic and consists of two phases (a) initial relief of pain, which is then followed by (b) a period of gradual resolution of the other signs of joint inflammation.

3. Pain relief is related to attainment of an effective mean serum phenylbutazone level, 3.09 ± 0.57 mg. per cent.

4. The pain relief afforded by a single large dose is not always sustained, and supplemental drug therapy is often required to maintain improvement and resolve the attack.

5. A recommended program for the use of oral phenylbutazone in acute gouty arthritis is (a) a large initial dose of 400 to 800 mg., followed by (b) intermittent administration of 100 mg. or 200 mg. four times daily for three days, or until the attack resolves.

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Review

The Effects of Digitoxin upon the Twelve Lead Electrocardiogram*

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NUMEROUS papers have been written on the effect of digitalis on the electrocardiogram. These have emphasized prolongation of the P-R interval,[1,2] lowering of the T waves,[2–5] depression of the S-T segments,[2–7] shortening of the Q-T interval,[3,4,8,9,10] and sharp return of the T wave from its peak to the iso-electric line.[4,9] With few exceptions[2,4,9,11] these papers have dealt with the standard limb leads only or with these leads plus one precordial lead. Since the aV limb leads and the six precordial V leads are now routinely employed in clinical electrocardiography, it is believed worth while to offer the present study of the effects of digitoxin upon the standard twelve lead electrocardiogram as recorded from ninety-one subjects.

MATERIALS AND METHODS

Subjects with normal or abnormal electrocardiograms were selected, and routine tracings were taken with the patient in the supine position before and after digitalization. Leads 1, 2, 3, aVr, aVl, aVf and V_1 through V_6 were recorded in each instance.

Digitalization was accomplished with oral digitoxin in amounts varying from 0.6 mg. in twenty-four hours in a four year old child to as much as 3.2 mg. in four days in an adult. Most of the subjects were given the glycoside in divided doses for one or two days, and the second electrocardiogram was taken not earlier than four hours after the last dose. Less than 16 per cent of the patients received less than 1.6 mg. of digitoxin; 88 per cent received the entire digitalizing dose in forty-eight hours or less.

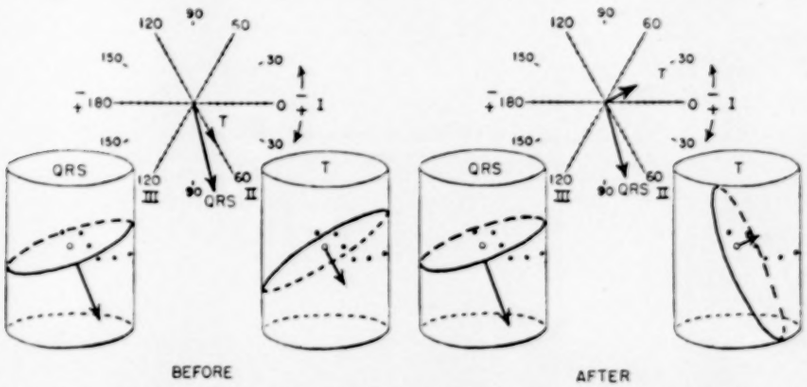

FIG. 1. Illustrates the frontal and spatial projections of the major QRS and T forces in a normal tracing before and after digitoxin. The electrocardiograms shown in Figure 6 were used to construct this figure.

The "electrical position" of the heart was determined by the major direction of the QRS vector. The tracings were arbitrarily classed as "vertical" when the frontal QRS vector was beyond +60 degrees on the triaxial reference system, "intermediate" when the vector lay between +60 and 0 degrees, and "horizontal" if less than 0 degrees.

The P-R and Q-T intervals were compared before and after digitoxin. All intervals were measured with needle point calipers, several complexes being meas-

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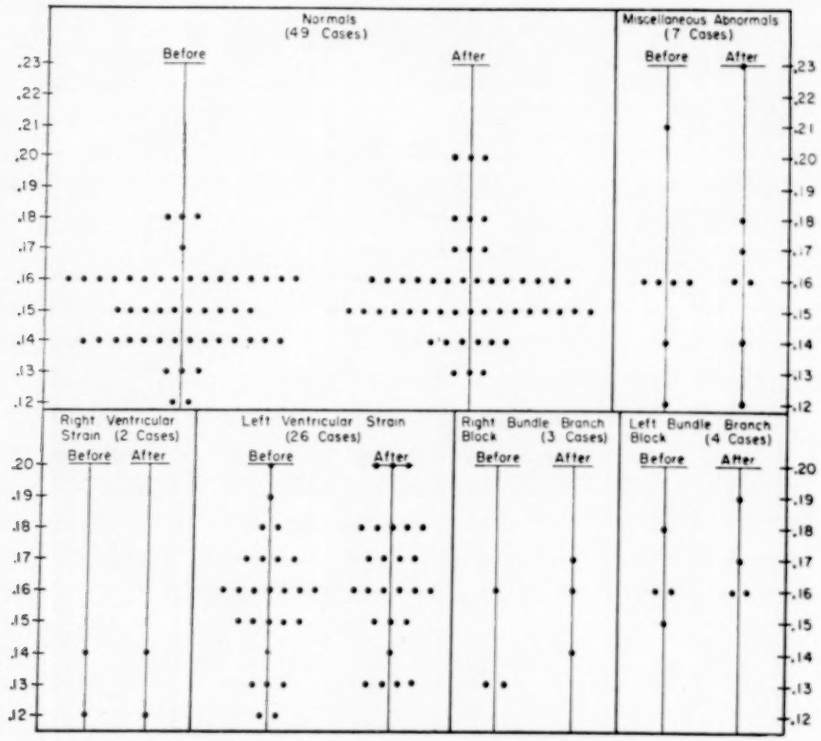

FIG. 2. P-R intervals before and after digitoxin.

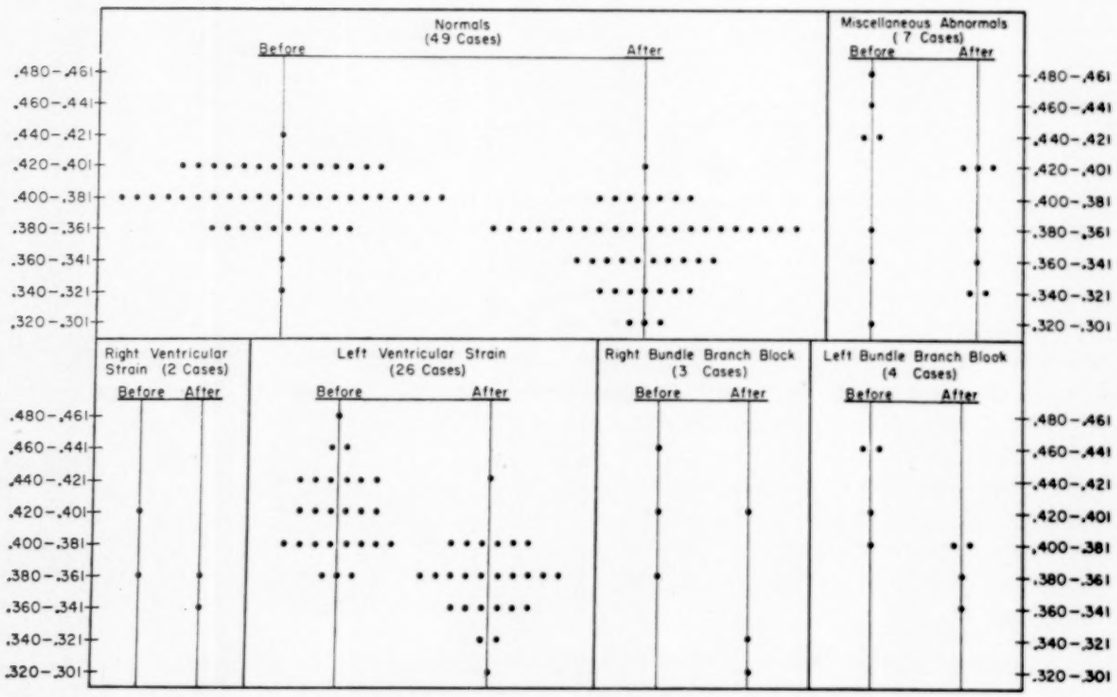

FIG. 3. Q-Tc intervals before and after digitoxin.

ured in each tracing. Whenever possible the Q-T interval was measured in leads with upright T waves. The Q-T was corrected for rate (Q-Tc) according to the formula of Bazett.[12] When the QRS interval exceeded .09 second, the Q-T interval was further corrected by subtracting the difference between the measured QRS interval and .09 second.[13,14] The normal value for Q-Tc was considered as 0.422 second for men and children, 0.432 second for women. S-T segment and T wave changes were compared in the standard limb leads, the aV leads and in the precordial leads.

The approximate direction of the frontal projection of the major QRS and T forces, and the angle between them, was determined by simple inspection of the tracings before and after administration of digitoxin. Utilizing the transitional complexes of the QRS and T waves in the V leads, the method described by Grant[15,16] was employed to determine the approximate spatial direction of these forces. (Fig. 1.) Although direction of vector forces can be ascertained by this method, their magnitude is not revealed. Differences in magnitude are apparent, however, on comparison of two tracings of the same patient, and in this fashion variations in magnitude can be considered.

RESULTS

A total of ninety-one subjects was used in the series. Of these, forty-nine had normal electrocardiograms, twenty-six showed the pattern of "left ventricular strain," two showed "right ventricular strain," three had right bundle branch block, four had left bundle branch block, and seven were abnormal for other reasons (Q-T interval prolongation in two, S-T segment changes in one, first degree A-V block in one, T wave changes in one, prolonged QRS conduction in two).

P-R Intervals. There was some over-all tendency toward lengthening of this measurement after digitoxin administration, as shown in Figure 2. With one exception, none was prolonged beyond 0.20 second despite the fact that in at least ten patients some degree of nausea developed from the glycoside. The exception was a patient whose P-R interval showed an increase from 0.21 to 0.23 second. Abnormal tracings tended to have a slightly longer initial P-R interval but other than this there was no real difference in response in the various groups.

Q-T Intervals. The corrected Q-T interval shortened in all groups. (Fig. 3.) The mean Q-Tc for the total group changed from 0.40 to 0.36 second. Certain quantitative differences, which appear in the comparison of the response of the two largest groups, are of especial interest.

Figure 3 graphically illustrates the distribution of Q-Tc in the normal group, before and after digitoxin administration, the mean values being 0.39 second before and 0.36 second after. The predigitoxin Q-Tc was prolonged in the left ventricular strain group (0.41 second) as compared to the predigitoxin normal group (0.39 second). After digitoxin, the Q-Tc measurement in the left ventricular strain group decreased appreciably from 0.41 second to 0.37 second, now closely approximating the same range as the digitalized normal group (0.36 second). The striking similarity of the distribution and range of the two groups after administration of digitoxin is seen in the chart. Thus the glycoside appears to have a greater effect upon the prolonged Q-Tc of the left ventricular strain group than upon the Q-Tc of the normal group. The same tendency was manifested also by the other abnormal groups. These observations are interpreted to indicate that digitoxin acts to force repolarization to take place at a maximally rapid speed, no matter what the initial rate.

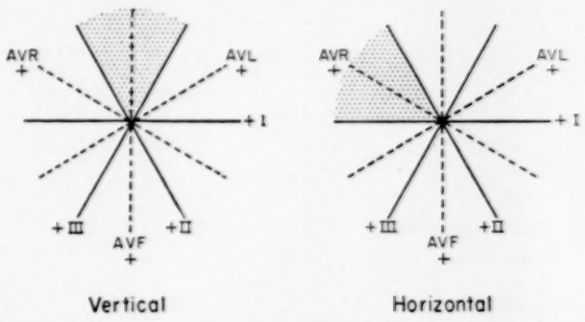

FIG. 4. Position of S-T segment vector after digitoxin.

Frontal and Spatial QRS-T Angles. There is an over-all tendency toward an increase in both frontal and spatial QRS-T angles, no consistent differences being apparent in the various groups. In about half of the normal group some widening was found, independent of the electrical position of the heart. Changes were more readily detectable in the left ventricular strain group, with an increase in angles in over 71 per cent and a decrease in about 13 per cent. Approximately the same results were obtained in the other abnormal groups in which there were enough examples to bring out this trend.

Magnitude of S-T Vector. The S-T segment vector was increased in fifty-three (58 per cent) of the ninety-one patients. Breakdown into various groups reveals that this increase is seen in the normal (55 per cent), left ventricular strain

TABLE I

S-T SEGMENT CHANGES AFTER DIGITOXIN ADMINISTRATION

	Leads							
	1	2	3	aVr	aVl	aVf	V right	V left
Normal subjects								
*Downward change:								
Horizontal	3	4	..	..	3	1	2	3
Intermediate	7	12	8	..	4	8	1	10
Vertical	4	15	15	..	..	20	3	20
†Upward change:								
Horizontal	..	..	2	4	..	..	..	..
Intermediate	..	..	..	8	..	..	..	..
Vertical	..	..	..	9	4	..	..	..
Left ventricular strain								
Downward change:								
Horizontal	5	4	..	..	5	..	4	7
Intermediate	7	10	3	..	6	7	3	8
Vertical	..	1	1	..	..	2	..	1
Upward change:								
Horizontal	..	1	3	3	..	1	2	..
Intermediate	..	..	1	8	..	..	3	1
Vertical	..	..	..	2	..	..	..	..
Right ventricular strain								
Downward change:								
Horizontal	..	..	..	..	..	..	..	..
Vertical	..	..	..	..	..	..	1	1
Left bundle branch block								
Downward change:								
Horizontal	1	2	..	..	1	..	..	2
Intermediate	..	1	1	..	..	1	..	..
Upward change:								
Horizontal	..	..	1	3	..	..	..	..
Intermediate	..	..	..	1	..	..	..	..
Right bundle branch block								
Downward change:								
Vertical	..	2	2	..	..	2	..	2
Upward change:								
Vertical	..	..	..	2	1	..	..	..
Miscellaneous abnormals								
Downward change:								
Horizontal	1	1	..	..	3	1	1	3
Intermediate	..	..	..	..	..	..	..	..
Vertical	..	..	..	..	..	..	1	..
Upward change:								
Horizontal	..	1	2	2	..	1	1	..

* Downward change signifies S-T segment less elevated, depressed or more depressed.

† Upward change signifies S-T segment less depressed, elevated or more elevated.

The terms horizontal, intermediate and vertical refer to the electrical position of the heart.

TABLE II

T WAVE CHANGES AFTER DIGITOXIN ADMINISTRATION

	Leads							
	1	2	3	aVr	aVl	aVf	V right	V left
Normal subjects								
*Downward change:								
Horizontal	6	5	1	..	6	3	5	6
Intermediate	17	17	15	2	9	17	14	18
Vertical	18	21	21	1	4	21	17	21
†Upward change:								
Horizontal	..	1	3	7	..	2	..	..
Intermediate	1	1	1	17	4	..	1	1
Vertical	..	..	..	21	12	..	1	..
Left ventricular strain								
Downward change:								
Horizontal	6	8	3	1	5	4	9	6
Intermediate	6	9	8	6	8	7	8	8
Vertical	..	1	1	..	..	1	1	1
Upward change:								
Horizontal	2	2	7	5	5	4	..	3
Intermediate	3	3	4	4	5	6	2	2
Vertical	1	..	..	1	1	..	..	..
Right ventricular strain								
Downward change:								
Vertical	1	2	2	..	1	2	..	2
Upward change:								
Vertical	..	..	..	2	..	..	..	..
Left bundle branch block								
Downward change:								
Horizontal	2	2	2	..	3	2	1	2
Intermediate	1	1	1	..	..	1	..	1
Upward change:								
Horizontal	..	..	..	2	..	..	1	..
Intermediate	..	..	..	1	..	..	1	..
Right bundle branch block								
Downward change:								
Vertical	1	2	2	..	2	1	1	2
Upward change:								
Vertical	..	..	1	2	1	..	..	..
Miscellaneous abnormals								
Downward change:								
Horizontal	4	2	1	1	4	1	4	4
Intermediate	1	1	1	..	1	1	1	1
Vertical	1	1	1	..	..	1	1	1
Upward change:								
Horizontal	..	..	2	3	..	1	..	..
Intermediate	..	..	..	1	..	..	..	..
Vertical	..	..	..	1	..	..	..	..

* Downward change signifies T wave less upright, flat, diphasic, inverted, more inverted.

† Upward change signifies T wave less inverted, flat, upright, more upright.

The terms horizontal, intermediate and vertical refer to the electrical position of the heart.

group (77 per cent) and left bundle branch block group (75 per cent), but not in those with right ventricular strain or right bundle branch block. This suggests that the S-T changes due to digitoxin are more readily apparent when the electrical activity of the left ventricle

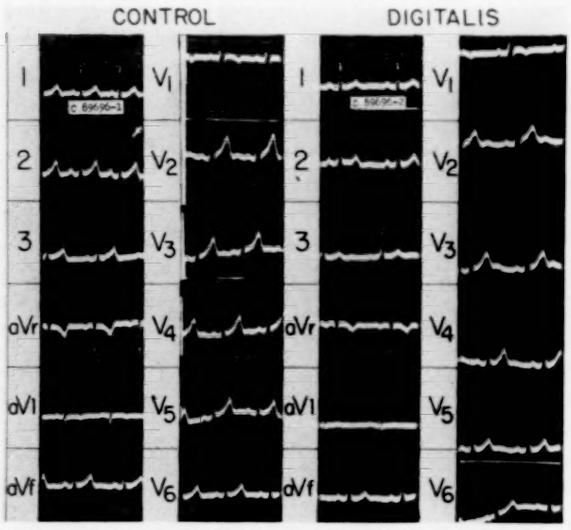

FIG. 5. Normal subject. Digitoxin 1.6 mg. was given in twenty-four hours, yet it is not possible to detect the effect of digitalis by inspection of the second tracing alone.

is preponderant. However, the total number of instances of right ventricular strain and right bundle branch block is too small to permit a definite conclusion.

Direction of S-T Vector. The S-T vector after digitoxin tends to point in a direction approximately opposite to that of the QRS vector. Thus in horizontal hearts the S-T segments were depressed maximally in leads 1, 2, aVl and precordial leads to the left of the transitional zone, V_5, V_6. In vertical hearts maximum depression was observed in leads 2, 3, aVf and the "left" precordial leads, principally V_5, V_6. These relationships may be seen graphically in Figure 4.

Upward changes in the S-T segments were most notable in the leads opposite to those already noted, such as lead aVr in nearly any position, lead aVl in vertical hearts, and lead 3 in horizontal hearts. Similarly leads from the right anterior chest also recorded an upward deviation of the S-T segment since the S-T vector was directed anteriorly, toward these leads. Downward change occasionally appeared in V leads to the right of the transitional zone (sixteen instances observed). A detailed tabulation of these changes is presented in Table I.

Magnitude and Direction of the T Vector. The T vector decreased in magnitude in 95 per cent of the normal group and in 71 per cent of the miscellaneous group. Both cases of right ventricular strain also showed this change. The other groups were variable, however, one-third of the left ventricular strain group and two-thirds of the right bundle branch block group showing an increase in magnitude.

In direction, the T vector tended to move away from the QRS vector, thus increasing the QRS-T angle in most cases.

T Waves. As the T vector was rotated away from the QRS vector the T waves were likewise changed to a direction opposite to the QRS waves. Thus in horizontal hearts, downward change in the T wave generally occurred in leads 1, 2 and aVl. In vertical hearts similar changes were seen in leads 2, 3 and aVf. An upward change in the T wave was most frequently observed in aVr but also was found in lead aVl in vertical hearts.

In precordial leads to the left of the transitional zone, as might be predicted from the positive QRS complexes, the T waves exhibited a "downward" directional change in most instances (seventy-three cases). Of particular interest was the observation that in leads to the right of the precordium the T waves also showed the same downward tendency, less marked in degree, in sixty-one instances even though the major QRS deflection was negative in these leads. A detailed tabulation of these changes is presented in Table II.

The T wave changes were often insignificant in appearance unless compared with the control tracing. Noteworthy is the fact that twenty-three of the forty-nine normal subjects could not have been diagnosed electrocardiographically as having received digitalis except by direct comparison of the two tracings. The postdigitoxin tracing in these cases appeared normal. (Fig. 5.) Serial tracings might have revealed greater change at other times[2] but it is well known from attempts at biological assay of digitalis in man that only certain patients show enough change in the T wave to permit successful use of this technic in digitalis standardization.

By contrast, marked changes were occasionally seen. In Figure 6 the postdigitoxin changes are not unlike those of digitalis effect superimposed

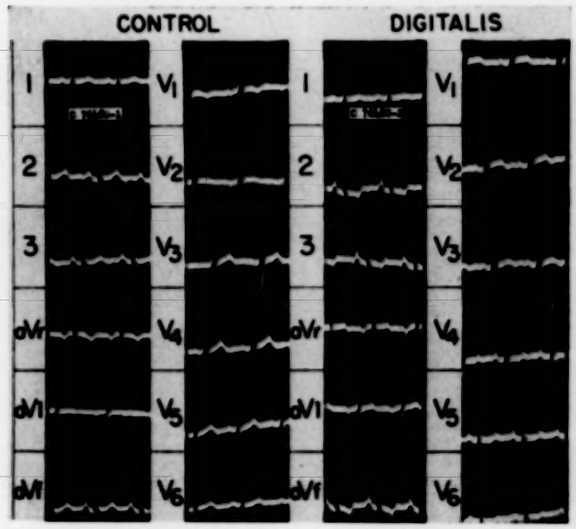

FIG. 6. Normal subject. "Vertical" electrical axis. Post-digitoxin effects are marked and resemble digitoxin effects superimposed on left ventricular strain.

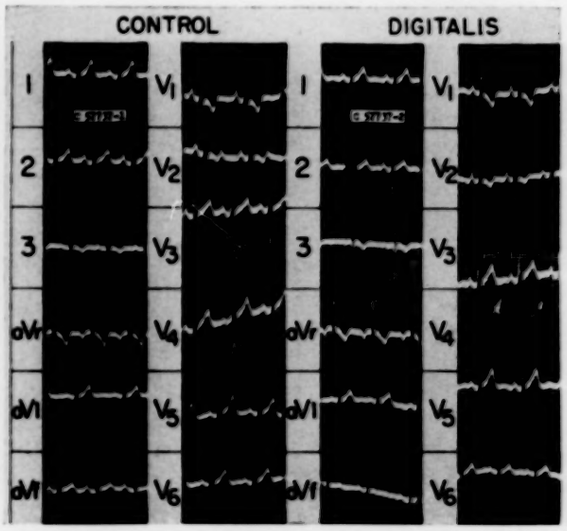

FIG. 7. Control record shows right ventricular strain pattern. Digitoxin effects are impossible to detect without the control tracing for comparison. Note also slight upward shift of the T wave in lead aVr.

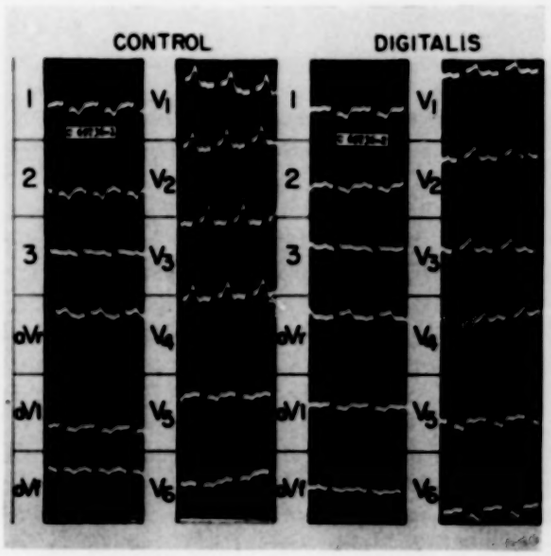

FIG. 8. Control tracing shows the left ventricular strain pattern. Except for the straight slope of the S-T segment and the short Q-T interval, the presence of digitoxin effect would be difficult to detect.

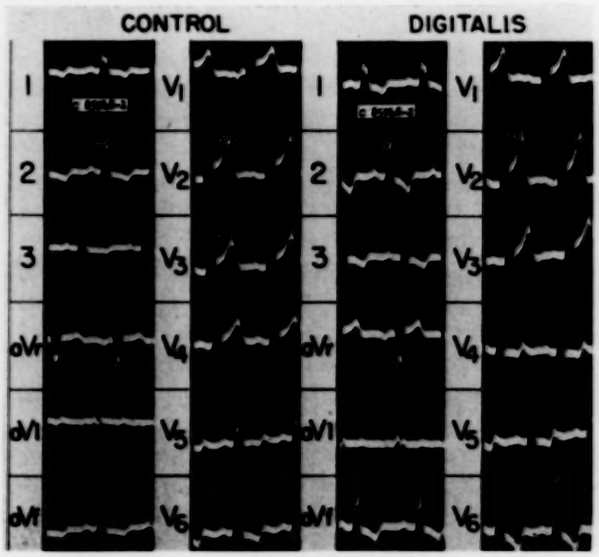

FIG. 9. Left bundle branch block. Note the increased depth of the T waves after digitoxin.

on left ventricular strain when the electrical axis is vertical. Similar effects were noted in four other persons in the normal group.

It is believed that one of the actions of digitalis glycosides is to accelerate repolarization and to cause this process to proceed in the same direction as depolarization. In addition to the shortening of the Q-T interval, the ST-T portion of the electrocardiogram is shifted in a direction opposite to the direction of the major QRS force. In situations such as left and right ventricular hypertrophy and the bundle branch blocks, in which the disease process has already produced ST-T shift opposite in direction from the QRS, the effect of digitalis is extremely difficult to detect. In such situations shortening of the Q-T interval is often the only effect which can be detected in the absence of a direct comparison of the pre- and postdigitalis tracings. Examples of such changes are seen in Figures 7 to 10. The well

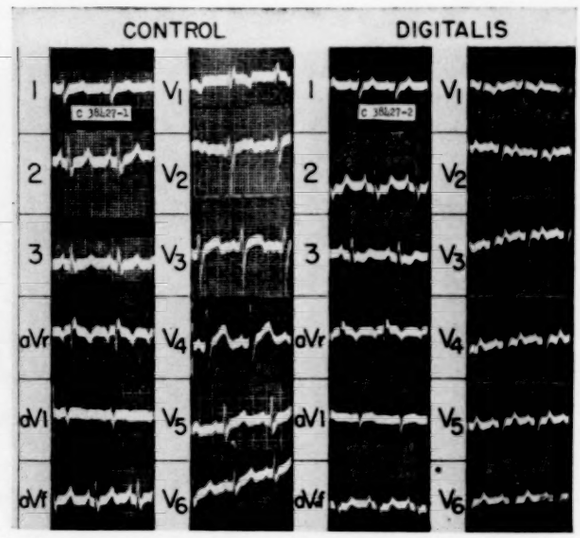

FIG. 10. Right bundle branch block. Digitoxin effect is difficult to detect in the absence of the control tracing.

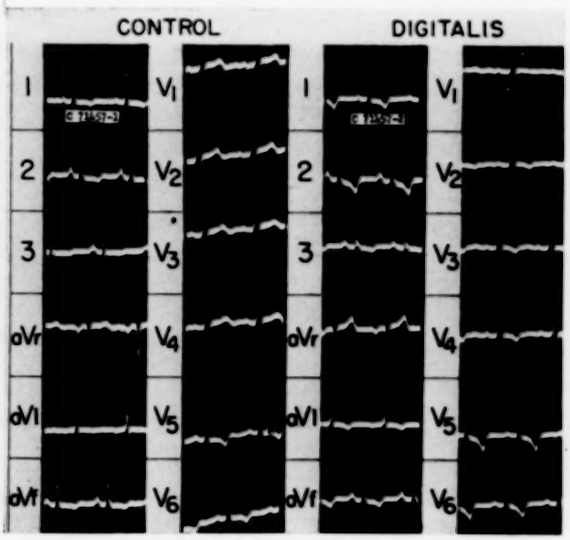

FIG. 11. Note the downward change in T waves to the right of the transitional zone, V_1, V_2, V_3 and V_4.

known straightening of the S-T segment as it merges with the T wave, as seen in Figure 8, is occasionally helpful in recognizing digitalis effect but unfortunately it is not clearly recognizable in a large number of tracings recorded in the digitalized state.

As might be predicted, all of the previously discussed effects of digitalis on the Q-T interval, S-T segment, T wave direction and T wave amplitude are not often found in a single tracing. Only one or two are frequently seen alone. It should also be pointed out that in some persons the change in the S-T and T portions of the electrocardiogram is not opposite in direction from the QRS. Thus the T wave may show an upward change in leads with upright QRS complexes, or a downward change in leads with downward QRS complexes. The explanation for such variations from the expected digitalis effect is not clear. Examples of such deviations are seen in Figure 7 in which slight upward change is seen in the T wave in aVr although the QRS is upright; in Figure 11 there is a downward change in the T wave in leads V_1, V_2, V_3, and V_4 in which the QRS is also downward in direction. Figure 11 also shows an example of unusually deep T wave inversion after digitalis administration.

SUMMARY AND CONCLUSIONS

The effects of digitoxin upon the standard twelve lead electrocardiogram recorded for ninety-one subjects have been analyzed. Tabulations and comparisons were made of the P-R intervals, the corrected Q-T intervals, the magnitudes of the S-T and T vectors, the individual lead S-T and T changes, and the frontal and spatial QRS-T angles.

The changes produced by digitoxin are: (1) mild lengthening of the P-R interval; (2) usually distinct shortening of the Q-T interval so that, regardless of type of electrocardiographic abnormality, the Q-T intervals are all brought within the same range as the normals; (3) widening of the QRS-T angles, more readily detected in the abnormals; (4) increase in the magnitude of the S-T vector, especially prominent in those tracings in which electrical activity of the left ventricle is preponderant, such as left ventricular strain and left bundle branch block; (5) change in the S-T segment in a direction opposite to the major QRS deflection; (6) decrease in the magnitude of the T vector, especially in normal tracings; (7) change in the T wave in a direction opposite to the major QRS deflection.

Other well recognized effects of the digitalis glycosides are straightening of the slope of the S-T segment from its origin to the region where it merges with the T wave, and relatively vertical slope of the T wave from its peak to the isoelectric line. These effects, along with the shortened Q-T interval and the ST-T changes generally opposite to the major QRS direction, are all consistent with the point of view that digitoxin acts to speed the repolarization process of ventricular muscle.

Since many of the electrocardiographic ST-T changes of ventricular strain and bundle branch block are similar to those of digitoxin effect, the latter are often not easily recognized in the presence of the former. Certain helpful changes may be present, however, particularly when two tracings are available for comparison. These are shorter Q-Tc interval, straighter slope of S-T segment, increased magnitude of the S-T vector and more vertical return of T from its peak to the iso-electric line. If the corrected Q-T interval is greater than .400 second, it is unlikely that digitoxin effect is present.

It has been pointed out that upon studying a single tracing in clinical practice, regardless of the general pattern, digitalis effect is difficult or impossible to detect in a surprising number of instances. Comparison of tracings made before and after digitalis administration demonstrates the drug effect far more clearly.

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Seminar on Diseases of the Pancreas

Acute Pancreatitis*

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ACUTE pancreatitis is a relatively common disorder which presents a continuous challenge to diagnostic ability and therapeutic resources. Advances in knowledge of the physiology of the pancreas and the pathogenesis of diseases of the pancreas and in management have resulted in a higher incidence of diagnosis and lowered morbidity and mortality.

Acute pancreatitis may be defined as an acute response of the pancreas to stress; the clinical picture varies with the extent of the reaction and the degree to which the function of the gland is impaired and adjacent structures are affected. There are three forms of pancreatic inflammation: (1) acute edematous or interstitial pancreatitis, in which edema is the outstanding lesion, (2) acute pancreatic necrosis and hemorrhage, and (3) acute suppurative pancreatitis, in which there is purulent exudate and abscess.

Acute pancreatitis was recognized at autopsy for many years before the first description in 1842 by Clässen[1] of several cases of inflammation of the pancreas. In 1850 Claude Bernard[2] injected oil and bile into the pancreatic ducts of experimental animals, thereby inducing acute pancreatitis. Friedreich in 1875[3] described the pathology of pancreatitis beginning with inflammation and hemorrhage and progressing to serous peripancreatitis, gangrene and abscess. Klebs[4] in 1876 described cysts and abscesses of the pancreas, which he thought originated in adjacent lymph nodes. He implied that hemorrhage might be caused by pancreatic juice. Balser[5] in 1882 was the first to recognize fat necrosis as resulting from inflammation of the pancreas. In 1886 Senn[6] produced acute pancreatitis in the dog by direct injury but was unable to correlate his results with clinical findings.

The classic American contribution to the subject was made by Reginald Fitz[7] who in 1889 produced a scholarly report based on seventy cases in the literature, of which twelve had been observed by him. He applied the fundamental anatomic knowledge already contributed of hemorrhage, necrosis, abscess, cyst and fat necrosis, and correlated the clinical picture. Pancreatic hemorrhage in which death rapidly ensued from one to thirty-six hours was clearly defined. Pancreatitis with hemorrhage into the interstitial tissue, and associated with pancreatic necrosis, was noted to result in death within two to four days. A longer course resulted in gangrene with death occurring in ten to eighteen days. He described suppurative pancreatitis in cases of abscess of the pancreas associated with chills, weakness and deterioration of general health. In one case, diabetes and fatty stools were noted, suggesting the development of a form of chronic pancreatitis as we recognize it today. Fat necrosis was not described. He outlined treatment, indicating that surgery was valuable in the drainage of abscesses but that exploration early in the disease might be injurious, especially because of the difficulty in establishing a correct diagnosis.

Following this first definitive report the underlying cause of pancreatitis became the object of intensive physiologic research. Fat necrosis was induced in the omentum of the dog by Langerhans[8] in 1891 by the injection of pancreatic juice, and he suggested that pancreatic lipase was the effective agent. Flexner[9] was able to find lipase in areas of fat necrosis.

In the next ten years considerable effort was expended towards the production of acute pancreatitis in the experimental animal. It is of interest that the lesion could be produced only by direct attack on the body and ducts of the pancreas after laparotomy. No worker was able to induce the process by drugs or indirect trauma. The net result of all the experimental

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work was to prove that pancreatic damage was produced by the escape of enzymes beyond their normal channels into the substance of the gland. A listing of these experiments by Siler and Wulsin[10] includes direct trauma, ligation of the pancreatic ducts, tying off the pancreatic arteries and veins, and the injection of bacteria, hydrochloric acid, succus entericus and irritant chemicals into the pancreatic ducts and parenchyma, all of which produced pancreatitis of varying degree.

TABLE I

ETIOLOGIC FACTORS IN PATIENTS WITH ACUTE PANCREATITIS

I. The gallbladder
   1. The common channel theory: reflux of bile into pancreatic duct due to obstruction of ampulla of Vater caused by
      a. Calculus at ampulla of Vater
      b. Spasm of the sphincter of Oddi
      c. Edema
   2. Obstruction to the flow of pancreatic juice by
      a. Gallstones in the pancreatic duct or
      b. Spasm of the biliary and pancreatic ducts secondary to disease of the gallbladder

II. The obstructive theory: blocking of pancreatic ducts by
   1. Stone
   2. Spasm of sphincter of ampulla of Vater or
   3. Papilla of Vater
   4. Spasm of pancreatic duct
   5. Edema of papilla of Vater and of pancreatic duct
   6. Tumor of pancreas
   7. Inflammation or fibrosis
   8. Epithelial metaplasia in the ducts
   9. Surgical ligature
   10. Duodenal diverticulum
   11. Ascaris
   12. Abnormalities of pancreatic duct system

III. Alcohol
   1. Ethyl
   2. Methyl

IV. Metabolic disturbances
   1. Hyperlipemia
   2. Diabetes
   3. Undernutrition
   4. Pregnancy
   5. Hemochromatosis

V. Trauma
   1. Accidental
   2. Surgical
   3. Electric shock

VI. Infection
   1. Specific infectious diseases
   2. Direct extension from foci in the abdomen

VII. Vascular

VIII. Allergic

IX. Neurogenic

The first attempt at explanation of etiology was made in 1901 by Opie[11] who, finding an impacted gallstone at the ampulla of Vater and a bile-stained pancreas, postulated that a common channel was created between the common bile duct and the pancreatic duct by the stone and that bile flowed into the pancreatic ductal system activating the pancreatic enzymes which caused the autolytic process. This concept, known as the theory of the common channel, has dominated medical thought for the past half century and is staunchly championed in the literature by many investigators. Opie was able to formulate this hypothesis on the basis of the work of Oser,[12] Körte,[13] and Lancereaux.[14] Each of these men, fortified by clinical observation, had indicated, independently of one other, his belief that gallstones in the terminal part of the common bile duct could act as a barrier to the outflow of pancreatic juice and allow bacteria from the inflamed common duct to enter the pancreatic duct and initiate pancreatitis.

Although Opie's work and thinking have stood the test of time, other etiologic factors have intruded themselves into the framework of complexities of etiology and pathogenesis. Supporters of each idea have attempted to prove that within their own concepts are the only causes of pancreatitis and that a unitary concept of etiology is possible. Each of the possible causative factors is undoubtedly capable of producing the disease, and each hypothesis may be true without implying that others are not. A reasoned consideration of all the causative factors would indicate that the pancreas is capable of responding to stress of many different types with a unitary reaction of varying degree.

Several authors have attempted to classify the various causative factors in pancreatitis, notably Dragstedt, Haymond and Ellis,[15] Jones,[16] and Siler and Wulsin,[10] and on the basis of their work this classification is presented. (Table I.)

PATHOGENESIS OF ACUTE PANCREATITIS

The Gallbladder. A. The common channel: Opie,[11] following the previously mentioned observations made at autopsy which led to the hypothesis of the common channel, proceeded to inject bile into the pancreatic ducts of experimental animals which responded with hemorrhage and necrosis in the pancreas. Archibald,[17] Baxter[18] and Popper[19] confirmed this finding.

Bile is generally accepted as a tissue irritant, but it is hardly likely that bile exerts its devastating effect on the pancreas without activation of pancreatic enzymes. The weight of

evidence suggests that trypsinogen is activated to trypsin. Powers, Brown and Stein[20] have shown by special methods of their own that the serum trypsinogen is increased in acute pancreatitis in dogs. Anastomosis was performed joining the common bile duct to the pancreatic duct, and spasm was induced by administering morphine. Pancreatitis resulted, with transition of edema to necrosis. Autopsy specimens revealed marked fibrosis and dilatation of the pancreatic duct. Bile pigment was present in the pancreatic duct and analysis of gallbladder bile showed a high concentration of trypsin.

Rich and Duff[21] have shown that other substances such as oil, india ink and soap may produce pancreatic reaction when injected into the pancreatic duct. They found that it was necessary to exert sufficient pressure to rupture the pancreatic ductules before pancreatitis resulted and that this force could hardly be developed in the human biliary tract. They analyzed twenty-three cases of acute pancreatitis and could find no evidence of ampullary stone or of bile in the pancreatic ducts. They concluded that the process was initiated by the escape of pancreatic juice into the pancreatic substance as a result of blockage of the ducts by epithelial metaplasia, with bulging into the lumen.

Opie's original observations suggested that a gallstone must be present in the ampulla before a common channel can be formed. Since many cases were seen in which no stones were present, additional theories were advanced. Archibald[17] thought that spasm of the sphincter of Oddi could, like a stone, occlude the openings of the common bile duct and the pancreatic duct, resulting in formation of a common channel. Balo and Ballon,[22] in reporting a case of acute pancreatitis in a patient with congestive heart failure, assumed that edema of the duodenal mucosa could occlude the ampulla and produce a common channel.

The theory of the common channel has been further fortified by various experiments and it is tempting to accept this explanation as the cause of acute pancreatitis. However, various objections have been raised. A fair number of patients have never had disease of the gallbladder. In most patients who have acute pancreatitis on whom surgery is performed, it is impossible to demonstrate a stone in the ampulla or in the pancreatic duct.

Opie dissected 100 cadavers and found that in eighty-nine the common bile duct and the pancreatic duct anastomosed before entering the duodenum. Mann and Giordano[23] were able to demonstrate a common channel in only 3.5 per cent of cases. Cameron and Noble[24] found an incidence of 75 per cent, and Rienhoff and Pickrell[25] reported that they could establish the presence of a common channel in 18 per cent of the cases they studied. Holzapfel[26] found a common channel in 20 per cent of fifty cases.

A major objection has been that the direction of flow in the biliary-pancreatic circuit may be from pancreas to common bile duct rather than the reverse. Experimental studies have indicated[27] that the secretory pressure of bile may reach 300 to 375 mm. of water, while the secretory pressure in the pancreatic duct ranges from 260 to 300 mm. This would favor the flow of bile from the biliary tree into the pancreas. However, Harms[28] has shown that in unanesthetized dogs at the height of digestion, the secretory pressure in the pancreatic duct is higher than in the biliary duct, thus permitting flow from the pancreas. The finding of substantial amounts of pancreatic enzymes in the bile duct drainage in patients who have a T-tube in the common duct after surgery would verify this point. Efforts have been made in human subjects who have T-tubes in the common duct after surgery to test the spasticity of the sphincter on the theory that in persons with hypertonic sphincters a common channel with biliary reflux is more likely to form. Colp and Doubilet[29] reported that, by injecting water under pressure into the common duct, a spastic sphincter was present when a pressure higher than 150 mm. of water was required for its opening.

Reflux of bile may be demonstrated by injection of opaque solution into the common bile duct with ensuing visualization of the pancreatic duct. Mallet-Guy[30] performed cholangiography on the operating table during biliary tract procedures and demonstrated a common channel in 21.6 per cent of cases. Hjorth[31] reported his own work and that of others and concluded that reflux may occur in 32 to 46 per cent of patients. Howell and Bergh[32] found reflux in 20 per cent of patients in whom postoperative cholangiography was done. Brahms did not observe visualization of the pancreatic duct in over 100 patients subjected to intravenous cholangiography.[33]

Recently, Gaillard[34] has reported acute pancreatitis following cholangiography through a T-tube. Hicken and McAllister,[35] in 100

operative and postoperative cholangiograms, noted reflux in every instance regardless of the relationship of the common bile ducts and the pancreatic ducts. Three patients showed symptoms suggestive of mild pancreatitis, and these investigators raised the interesting question of whether or not reflux occurs as a normal physiologic process without inducing any pancreatic response. Their experience has not been duplicated by other observers.

These reports would indicate that biliary reflux into the pancreas can occur as a result of sphincter spasm. It is apparent that pancreatic reflux into the biliary tree can also occur, as Hjorth[31] found; he subsequently suggested that reflux of pancreatic juice could cause cholecystitis and cholelithiasis.

B. Gallbladder disease in the absence of a common channel: While some disagreement exists as to the common channel mechanism in acute pancreatitis, most observers agree that a large percentage of patients with acute pancreatitis have associated disease of the biliary tract. Molander and Bell,[36] in an analysis of 158 cases of acute pancreatitis, found that disease of the gallbladder was present in one-third of the male cases and two-thirds of the female patients, an incidence six times higher than in normal subjects. Paxton and Payne[37] found an incidence of 41 per cent and Schmieden and Sebening[38] 70 per cent. A compilation of 667 cases of acute pancreatitis, as reported by various authors,[39] showed 367 to have gallstones.

The significance of this relationship of gallstones to pancreatitis in those cases in which a common channel is present is clear. The significance of gallstones in the absence of a common channel is not so clearly understood and the hypothesis must be advanced that a stone at the ampulla, or spasm of any of the structures at the ampulla, such as the common bile duct, the sphincter of Oddi or the pancreatic duct, may act to obstruct the flow of pancreatic juice, thereby inducing pancreatitis. One may postulate that spasm of these structures may be initiated by a diseased gallbladder through a vago-vagal reflex, since the gallbladder and the pancreas are innervated by the vagus nerves.

Obstruction as a Cause of Pancreatitis. Rich and Duff[21] found in a study of twenty-four cases of acute hemorrhagic pancreatitis that narrowing and obstruction of the pancreatic ducts were present in thirteen, or 54 per cent. The immediate cause of the narrowing was metaplasia of the epithelium of the pancreatic duct. The same epithelial changes were demonstrated in 18.6 per cent of 150 consecutive autopsies of persons over twenty-five. Yotuyanagi[40] found ductal metaplasia in 50 per cent of normal pancreatic glands in autopsy material.

Rich and Duff stated that these metaplastic changes in the duct walls could produce obstruction of the flow of pancreatic juice and if the ductal pressure were sufficiently elevated, rupture of the smaller ducts could occur. The extravasation of secretion into the parenchyma could result in activation of trypsinogen to form trypsin with resultant digestion of the pancreas. They also suggested that this situation of obstruction and oversecretion might be present in persons who suffered an attack of acute pancreatitis after indulgence in alcohol or a heavy meal, at which time pancreatic secretion is at its height. Instances of acute pancreatitis after alcohol are frequently reported, and a recent case report by McDermott, Bartlett and Culver[41] described acute pancreatitis in a young college student who indulged in a dietary orgy following a prolonged fast.

Other investigators have been able to produce varying degrees of acute pancreatitis in animals. Popper and Necheles,[42] after partially ligating the pancreatic ducts in dogs, administered secretin and produced pancreatic edema. Hemorrhage and necrosis could not be produced until the superior pancreaticoduodenal artery was occluded.[43] Lium and Maddock[44] ligated the pancreatic ducts in cats and administered pancreatic secretory stimulants, such as secretin, pilocarpine and mecholyl, and produced pancreatic changes varying from edema to necrosis. Their experiments were similar to those originally performed by Opie in 1901 and their results were parallel with his. Opie realized that obstruction of the pancreatic ducts could lead to pancreatitis, but of lesser severity than that produced by bile injection.

Pancreatic ductal obstruction seems to be a logical explanation for the production of acute pancreatitis but other factors are necessary, such as a hypersecreting gland and perhaps some impairment of the pancreatic circulation. Certain objections are evident. Acute pancreatitis is rare in persons who have undergone surgery for carcinoma of the pancreas, at which time the ducts are ligated or sutured to the intestinal wall. Naffziger and McCorkle[45] reported elevated serum amylase after resection of the head of the

pancreas for carcinoma but no evidence of pancreatitis appeared.

Radakovich, Pearse and Strain[46] conducted a series of experiments in dogs in which the ducts were ligated, secretin was administered and an oily emulsion injected into the superior pancreaticoduodenal artery. They were unable to produce acute hemorrhagic pancreatitis.

However, despite the fact that clinical pancreatitis does not always occur with obstruction of the ducts, or that pancreatitis cannot be produced in laboratory animals uniformly by obstruction of the ducts, the factor of obstruction of the pancreatic duct must be considered to play an important part in the pathogenesis of the disease. This obstruction may be due to stone, spasm, tumor or fibrosis, or to epithelial metaplasia.

The obstructive theory is attractive in that the various degrees of acute pancreatitis can be easily explained. As first suggested by Rich and Duff,[21] pancreatic juice in the presence of obstruction escapes into the interstitial tissue. Trypsinogen in contact with tissue and tissue juice becomes activated into trypsin which initiates necrosis of the walls of the smaller blood vessels, resulting in hemorrhage. Necrosis is produced by lipase. Elman[47] suggested that with minimal stress to the pancreas, pancreatic edema might develop.

Obstruction to the pancreatic duct may be caused by ascaris. Duncan[48] has described a fatal case of acute pancreatic necrosis and abscess in an infant eighteen months old. The abscess cavity contained the remains of an adult ascaris and the stools contained ascaris.

Obstruction may also be produced by surgical ligature.[49] Ogilvie[50] described three cases of acute pancreatitis accompanied by perivaterian duodenal diverticula. He assumed that inflammation and swelling of these diverticula could obstruct the pancreatic duct and thereby induce pancreatitis.

Pancreatitis Due to Alcohol. Next to disease of the gallbladder, alcohol is listed as the second most common cause in most reported cases of acute pancreatitis. One of the first writers to call attention to alcohol and pancreatitis was Friedreich[3] who stated in 1878: " . . . a general, chronic interstitial pancreatitis may result from excessive alcoholism (drunkard's pancreas)." Fitz[7] mentioned that many cases "were addicted to the abuse of alcohol." Halsted[51] in 1901 described a case of pancreatitis which at autopsy revealed a stone impacted in the ampulla of Vater and he suggested that two additional factors, "adiposis and excessive use of alcohol," might be implicated in the etiology of pancreatitis. This was the case upon which Opie based his common channel theory. Opie[11] in 1902 commented upon the association of pancreatitis and chronic alcoholism. Lefas[52] in 1900, Lando[53] in 1906, and Poggenpohl[54] in 1909 directed attention to the history of alcoholism in persons with pancreatitis but no pathogenic explanation was deduced.

The importance of alcoholism in precipitating attacks of acute pancreatitis has been realized by many investigators. Egdahl[55] described a group of 105 patients who had acute pancreatitis, seventeen of whom had imbibed large quantities of alcohol prior to onset of the illness. Symmons[56] in 1917 studied a series of thirty-one sudden unexplained deaths in persons who had apparently been in good health, although they were addicted to alcohol; all had died of acute hemorrhagic pancreatitis. Postmortem examination did not reveal disease of the gallbladder in any case. Macnie[57] in 1932 and Adams and Boulous[58] in 1933 also reported cases of sudden death during alcoholic bouts, and in these instances, too, autopsy disclosed acute hemorrhagic pancreatitis without disease of the gallbladder.

McWhorter,[59] reporting sixty-four cases of acute hemorrhagic pancreatitis, noted that seven (11 per cent) gave a history of heavy drinking prior to inception of the illness. Myers and Keefer[60] in 1934 found that six (21 per cent) of twenty-nine patients with acute pancreatitis were alcoholics. Rich and Duff[21] in 1936 recorded seven (29 per cent) of twenty-four cases as having been precipitated by alcoholic indulgence.

A careful review by Weiner and Tennant[61] in 1938 of thirty-eight cases of acute hemorrhagic pancreatitis encountered in a series of 4,000 autopsies revealed that twenty-five (66 per cent) became ill shortly after an alcoholic spree. Included in this large series was a group of fifty-one patients who died of acute alcoholism. Twenty-seven (53 per cent) of these were found to have disease of the pancreas. Of forty-one chronic alcoholics on whom autopsy was performed for a variety of causes, nineteen (47 per cent) had chronic lesions of the pancreas. Clark[62] in 1942 studied the autopsy protocol of thirty-six habitual drinkers who died in acute alcoholic states and found that fifteen (42 per cent) died of

acute hemorrhagic pancreatitis. Of 150 routine autopsy examinations of alcoholic subjects twenty-seven (18 per cent) showed microscopic evidence of pancreatitis. Clark was impressed by the absence of disease of the biliary tract in most cases. He stated that "the role of prolonged alcoholic debauch in the pathogenesis of pancreatitis appears of striking importance." Paxton and Payne[27] reported an 18 per cent incidence of alcoholism in a group of 307 cases of acute pancreatitis. Bockus and Raffensperger[63] found the incidence in their series to be 50 per cent.

Carter,[64] in a study of eleven alcoholic patients hospitalized in a city ward for acute abdominal pain, established a diagnosis of acute pancreatitis in each case by the demonstration of elevation of the serum amylase. Four patients were operated upon and the diagnosis was substantiated by gross and microscopic observations. Carter postulated that the *modus operandi* was gastritis and edema of the duodenal mucosa. Domzalski and Wedge[65] in 1948 compared random blood serum amylase values obtained from fifty alcoholic patients with those from a control group of fifty non-alcoholic patients. Twelve of the alcoholics (24 per cent) showed elevated serum enzyme values, while only one of the control subjects (2 per cent) presented a high blood amylase. The observations of Carter and Domzalski suggested to both investigators that alcoholics suffer from repeated mild or subclinical attacks of acute pancreatitis, and also that these episodes may eventuate in chronic relapsing pancreatitis.

Despite the almost inescapable conclusion that alcoholism, even in the absence of disease of the biliary tract, may be a direct cause of pancreatitis, little investigative work has been done which permits elucidation of the etiologic mechanism. Pancreatitis has not been produced with alcohol in experimental animals. Various explanations of the etiologic relationship, however, have been offered. Egdahl[55] suggested that gastroenteritis produced by alcohol might be responsible for pancreatitis. Myers and Keefer[60] advance the possibilities (1) that alcohol in the blood might damage the pancreas directly, (2) that duodenal congestion might obstruct or infect the ducts, or (3) that persistent vomiting might cause regurgitation of the duodenal contents into the pancreatic ducts.

Rich and Duff,[21] commenting on the clinical observation that many cases of acute pancreatitis occur after a heavy meal or large alcoholic intake, postulated that alcohol or food coming into contact with the duodenal mucosa might stimulate secretion from the pancreas in proportion to the intensity of the stimulus. Following heavy meals or excessive alcoholic intake, pancreatitis might result when excessive pancreatic flow occurred against some resistance in the pancreatic duct system. Alcohol could produce pancreatitis by obstruction due to duodenitis and inflammation of the papilla associated with pancreatic hypersecretion.

Recent reports offer still another possible role of alcohol in the etiology of pancreatitis, namely, the protein and vitamin deficiencies seen in chronic alcoholics. Malnutrition in young African children has been shown to produce kwashiorkor, a disorder characterized by fatty liver and fibrotic changes in the pancreas.[66] Veghelyi, Kemeny, Pozsonyi and Sos[67] found that infants maintained on deficient diets showed evidence of defects in pancreatic secretion which could be relieved by the addition of milk to the diet. The observation has been made that large doses of methionine can prevent morphologic changes in the pancreas resulting from the feeding of a high fat, low protein diet to animals.[68,69]

The effect of alcohol on pancreatic secretion has been studied by a number of physiologists. Bayliss and Starling,[70] on the basis of their original work with secretin in 1902, concluded that alcohol could stimulate the formation of this hormone by direct action on the duodenal mucosa. Kuwschinski[71] even earlier (1888) had shown that alcohol given to animals by mouth increased the volume of pancreatic flow. Fleig[72] in 1903 demonstrated an increase in pancreatic secretion by placing alcohol in an isolated loop of small intestine. Zitovitch[73] in 1905 was able to increase the pancreatic flow by intraduodenal administration of alcohol. Gizelt[74] in 1906 made the most extensive investigations in animals. His studies showed that the effect on the pancreas was not due solely to the presence of alcohol in the duodenum and small intestines. Pancreatic secretion could be stimulated in animals by the instillation of alcohol into the isolated stomach or into the rectum. Gizelt suggested on the basis of these findings that alcohol had a direct action on the pancreas.

Alcohol is a stimulus to gastric secretion not only when administered orally, as in the commonly used alcohol test meal, but also when it is

given intravenously, through the rectum or when perfused through an isolated loop of small intestine.[74] The gastric juice obtained under all of these conditions is high in acid and low in pepsin. Experiments by Newman and Mehrtens[75] indicate that alcohol acts via the elaboration of a histamine-like substance. Dragstedt[15] has shown that diluted alcohol perfused through the lung liberates histamine.

The increase in volume of pancreatic secretion when alcohol is given orally can be explained by the following premise: Alcohol in the stomach stimulates the elaboration of hydrochloric acid and histamine; the increased acid finds its way into the duodenum where secretin formation is heightened; in addition, secretin production results from the direct action of alcohol on the duodenal mucosa. It is also possible that the histamine produced in the stomach, when absorbed, may act as a direct pancreatic stimulant via the blood stream. MacKay[76] has stated that histamine is a mild direct pancreatic stimulant but this has not been corroborated by other investigators.

In tracing the pathogenetic relationship to its completion, the factor of obstruction of the pancreatic duct must be dealt with. McGowan, Butsch and Walters[77] have shown that hydrochloric acid and alcohol when passing into the duodenum (after oral ingestion of alcohol) cause spasm of the sphincter of Oddi. After large quantities of alcohol have been taken orally, edema of the duodenal mucosa and papilla of Vater may also occur. This edema has been noted at the autopsy of alcoholic subjects. Dreiling, Richman and Fradkin[78] have suggested that oral intake of alcohol causes the pancreas (via the secretin mechanism) to secrete a large volume of juice against an obstruction produced by spasm and edema of the papilla. This reasoning is compatible with the hypersecretion-obstruction theory. Another possibility is that the chronic undernutrition of alcoholics produces a situation analogous to that of ethionine pancreatitis.

Bockus, Kalser, Roth, Bogoch and Stein[79] have tried to establish points of differentiation between the pancreatitis due to alcohol and that due to biliary disease. There seems to be no pathologic difference and identification of the cause by the anatomic state is impossible. However, on clinical grounds they conclude that alcoholic pancreatitis is a more severe disease which has a greater incidence of complications and recurrences and has a poorer prognosis. Relapsing pancreatitis and pancreatic calcification occurred far more often in the group of alcoholic subjects.

The role of methyl alcohol in the production of acute pancreatitis has been reviewed by Bennett et al.[80] They treated 323 patients who had imbibed bootleg whiskey containing wood alcohol. Severe abdominal pain, nausea and vomiting were noted in most patients. One of the most striking laboratory observations was an elevation in serum amylase (above 300 units) in fourteen of twenty-one patients on whom amylase tests were performed. This elevation persisted for as long as a week in most patients, gradually returning to normal. These findings assumed great importance against the background of the discovery of pancreatic necrosis in thirteen of seventeen subjects who underwent autopsy. In these cases most of the pancreatic damage seemed to be secondary to vascular injury and hemorrhage. Keeney and Mellinkoff[81] reported that mild congestion and parenchymal hemorrhage in the pancreas in one of six fatal cases were noted at autopsy.

Burhans[82] discovered acute hemorrhagic pancreatitis in every one of eleven cases of methyl alcohol poisoning and suggested that pancreatic necrosis is a feature of most fatal cases of methyl alcohol poisoning. This may be due to a direct toxic effect on the pancreas. Bennett[80] suggests interference by methyl alcohol with controlling enzyme systems so that bicarbonate production is depressed. In view of recent evidence of the role of carbonic anhydrase in pancreatic secretion, it is tempting to suggest that some interference with pancreatic secretion results.[83]

Pancreatitis Due to Metabolic Disturbances. A. Hyperlipemia: Klatskin and Gordon[84] recently described a case of recurrent acute pancreatitis associated with lipemia and pointed out the relationship of lipemia to this disease. Hyperlipemia may not be noted until the patient has suffered several attacks of clinically documented acute pancreatitis. Occasionally hyperlipemia is associated with skin xanthomatosis and lipemia retinalis. These workers upon gross examination found lipemic serum containing a marked increase in neutral fat, the concentration ranging between 13.0 and 46.0 mEq./L. (normal about 2.0 mEq./L.). Hypercholesterolemia was noted, and several members of the family were found to have hyperlipemia, due primarily to a marked increase in neutral fat. Klatskin and

Gordon[84] suggest that pancreatitis may be caused by hyperlipemia due to deposition of xanthomatous masses in the pancreas, or to atherosclerotic vascular lesions, or to actual fat emboli within the pancreatic vessels. They cite Moreton's work[87] on the association of high chylomicron counts (which were present in Klatskin and Gordon's case) and the development of atherosclerosis.

Experimental evidence advanced by Binet and Brocq[85] does not support the hypothesis that disease of the pancreas produces hyperlipemia. Dragstedt's work on lipotropic factor (lipocaic) deficiency in pancreatic disease[86] does not seem to be an adequate explanation for the few cases (only fifteen) of pancreatitis with elevated blood lipids.

B. Diabetes: Diabetes as a pathogenetic factor in pancreatitis has been discussed by Bossak and Joelson[88] who found eight instances of acute pancreatitis in 106 patients with diabetes mellitus. In only one of these patients was marked arteriosclerosis noted at autopsy. They postulated that some lesion of the smaller arterioles or capillaries might be provocative or that ischemia due to vasospasm might be the cause.

C. Undernutrition: Popper[89] suggests that the most important etiologic factors in acute pancreatic necrosis in man are protein deficiency, excessive pancreatic enzyme stimulation and obstruction of pancreatic ducts. Degeneration and inflammation of the pancreas not due to factors in other organs are related to abnormalities of secretion, activation and flow of the pancreatic enzymes. The pancreas appears to be peculiarly susceptible to protein deficiency, perhaps because of the large quantity of protein required for the copious pancreatic enzyme formation. This may occur with a low protein diet, as seen in kwashiorkor.

Farber and Popper[90] have produced interstitial inflammation and necrosis of pancreatic acini and fat by feeding ethionine to rats. Ethionine is antagonistic to methionine and inhibits protein synthesis. They suggest that undernutrition in man may play a role in disorders of the pancreas by interfering with enzyme formation. Morphologic changes have been noted in the pancreas in chronic debilitating states such as ulcerative colitis[91] and ileitis.[92]

D. Pregnancy in relation to pancreatitis: Pancreatitis occurring during and immediately after pregnancy has been described and may be assumed to be related to the presence of disease of the biliary tract or to stasis within the biliary tract or the duodenum. Joske[93] recently reported six patients who had pancreatitis following pregnancy, four of whom required cholecystectomy and one a T-tube drainage; in a sixth patient the condition subsided without operation. Fitzgerald[94] studied pancreatic function in pregnant women and found a decrease in enzyme secretion, deducing that pancreatitis in these circumstances might occur as the result of a rebound, that is, overproduction of enzymes.

Millen, Russ, Eder and Barr[95] have suggested that pancreatitis in pregnancy may be the result of hyperlipemia. They reported a patient who developed acute pancreatitis shortly before delivery and in whom markedly elevated serum lipids were present. They expressed doubt, however, as to whether or not pancreatitis was responsible for the accumulation of neutral fats in the plasma.

E. Hemochromatosis: In hemochromatosis, fatty infiltration and fibrosis of the pancreas, with deposits of hemosiderin in the acini, the ducts, the islets of Langerhans and connective tissue produce a form of chronic pancreatitis. The obstruction secondary to these factors may cause abdominal pain secondary to that of acute pancreatitis.

Traumatic Pancreatitis. A. Accidental: Traumatic rupture of the pancreas was first reported by Travers[96] in 1827; his patient was a coachman who suffered a compression injury of the abdomen. Acute pancreatitis may follow trauma of any degree. The pancreas lies deep in the abdomen and is fairly well protected against injury, but if the abdominal muscles happen to be flaccid at the time the pancreas may be crushed against the vertebrae. Stern[97] described eight cases of traumatic pancreatitis, including a patient of his own who recovered. He noted associated elevated serum amylase values. Keyes[98] reported a case due to a blast from an underwater explosion; he emphasized that even mild force may produce damage and that other organs, especially the duodenum and jejunum, may be involved. Phillips and Seybold[99] classified the types of trauma as (1) penetrating, due to stab and gunshot wounds, (2) subcutaneous, as from falls, blows and crushing injuries (including that from a steering wheel), and (3) surgical. The mechanism is assumed to be rupture of the capsule of the pancreas with release and activation of enzymes. The elevation of serum amylase is marked.

B. Surgical: Surgical pancreatitis is of great interest. The pancreas may be traumatized directly or, as Millbourn[100] has shown, by injury to the pancreatic duct in dissecting a duodenal ulcer during subtotal gastrectomy. He found elevations of blood amylase postoperatively in a large number of patients subjected to gastrectomy for duodenal ulcer. These findings were encountered in association with a clinical picture of acute pancreatitis. Most patients who underwent gastrectomy for gastric ulcer or carcinoma did not show either clinical or laboratory signs of pancreatitis. Cattell and Warren[49] have noted that the accessory duct of Santorini is most vulnerable to surgical injury and that the consequences of such injury depend upon the size of the duct, the character of the injury (laceration, division or ligation), the type of sutures and the functional state of the pancreas in the immediate postoperative period. These authors suggest duodenal stasis as a cause, but others consider obstruction of the flow of pancreatic juice as a cause. Acute pancreatitis has occurred after surgery of the biliary tract. Brown[101] has reported two cases of acute hemorrhagic pancreatitis following common duct exploration and quotes Blumensaat[102] who states that postoperative pancreatitis is not uncommon, probably being due to trauma, congestion and infection.

Perryman and Hoerr[103] found elevations of serum amylase in twenty-seven of eighty-five patients undergoing surgery on the upper gastrointestinal tract and biliary tract, an incidence of 46 per cent in gastric operations, 35 per cent in common bile duct explorations and 33 per cent in direct procedures on the pancreas. There were two fatalities. These authors suggest that pancreatitis may occur in the mild form as a result of the manipulation.

Robinson[104] has observed the development of acute pancreatitis in a patient who had undergone translumbar aortography. Since there seemed to be no reason for the needle to have touched the pancreas, he assumed that the lesion was due to excessive concentration of the dye in the celiac axis and thence through the pancreatic artery to the pancreas.

C. Electric shock: Pancreatitis has occurred in persons who have experienced electric shock, as reported by Glazier[105] in three soldiers who were electrocuted accidentally. Sirolli[106] has described extensive hemorrhage and necrosis in animals dying of electric shock.

Infection as a Cause of Acute Pancreatitis. Acute pancreatitis occurs during scarlet fever, typhoid fever, generalized sepsis, diphtheria, mumps and other virus diseases[107–110] and is assumed to be the result of blood-borne infection. Egdahl[55] has described eleven cases due to mumps, two with typhoid, two with appendicitis, one with furunculosis, one with malaria, one with syphilis and one with pulmonary tuberculosis. Brahdy and Schaffer[111] reviewed 7,054 cases of mumps and found 171 cases of acute pancreatitis, an incidence of 2.4 per cent.

Maugeret,[112] supported by Judd,[113] stated that bacterial infection may spread from the wall of a diseased gallbladder to the pancreas by ramification through the anastomosing network of lymphatics in the retroperitoneal tissue between the gallbladder and the pancreas. Kaufmann,[114] however, was unable to produce pancreatic necrosis in experimentally induced acute bacterial cholecystitis in animals. Wangensteen[115] commented on the relative safety of the non-surgical treatment of acute cholecystitis, and Kodama[116] was unable to demonstrate any direct lymphatic connection between the gallbladder and the pancreas.

Vascular Factors. Rich and Duff[21] described a specific vascular lesion in acute pancreatitis. They noted changes in the media and necrosis of the walls which might be a causative factor. Smyth[117] indicated that any vascular lesion is the result of the disease and not the cause. He injected mercury into the pancreatic artery of dogs, and focal areas of acute pancreatic necrosis resulted. However, he did not note a spreading type of pancreatitis. Even if pancreatic secretion was stimulated by food or mecholyl, these focal areas remained localized. Block, Wakim and Baggenstoss,[118] seeking to determine the relationship of vascular factors to the pathogenesis of pancreatitis, obstructed the pancreatic ducts of rats and produced edema, inflammation, degeneration, atrophy of acini and fat necrosis. Production of ischemia resulted in progression to hemorrhagic necrosis. Complete devascularization of large portions of the pancreas resulted in ischemic infarcts, but occasionally a focal form of acute pancreatitis did result only from prolonged, severe and extensive ischemia. The work of Popper, Necheles and Russell[43] has already been cited.

Recently, acute pancreatitis has been observed in disseminated lupus erythematosus. The necrotizing vascular lesion of lupus was present

in the pancreatic vessels.[119] Occasionally an artery or an aneurysm may rupture into the pancreas (apoplexy of the pancreas) with ensuing hemorrhagic necrosis.[120]

From these experimental observations it is apparent that interference with the pancreatic circulation alone does not result in acute hemorrhagic or necrotic pancreatitis unless some additional factor, such as obstruction or hypersecretion, is present. Milder changes, such as edema, may occur as a result of vascular interference.

Allergic Factors. Following up these reports on vascular changes, Thal and Brackney[121] were impressed with a similarity to the vascular lesion in the dermal Shwartzman reaction. This consists of diffuse hyaline capillary thrombosis and extensive necrosis of arterioles, venules and larger vessels, associated with hemorrhage, thrombosis and cell inflammation. Thal and Brackney injected meningococcus toxin into the pancreatic duct of rabbits and goats. Twenty-four hours later, diluted meningococcus toxin was injected intravenously. Invariably acute pancreatic necrosis resulted. As a result of this work the following hypothesis was advanced. Toxins in the bile or duodenal contents may sensitize the pancreatic blood vessels. As shown by Shwartzman, the reaction is then produced in sensitized tissue by the presence in the systemic circulation of a number of biologically unrelated substances. While this idea seems logical, no clinical evidence has yet been advanced to support it.

Shaffer[122] describes the case of a forty-eight year old man in whom acute pancreatitis developed at the time of an attack of giant urticaria. The diagnosis was substantiated by a serum amylase of 300 units and the fact that the patient had undergone exploration for acute pancreatitis four years before the present attack. The response of this patient's abdominal symptoms to pyribenzamine® was dramatic.

Neurogenic Factors. Wener, Simon and Hoff[123] produced acute pancreatitis in dogs by administering a cholinergic agent, mecholyl.® It is conceivable that stress in a human subject might render that person more vulnerable to pancreatitis, with sphincter spasm as the mode of production. Excessive enzyme production in the presence of this spasm could be an added factor.

Anomalies of the Pancreatic Ducts. Hughes[124] has recently reported a patient who had acute pancreatitis in whom obstruction of the pancreatic duct system resulted from anomalous location of the common bile duct. At autopsy it was revealed that the common duct had a separate opening into the duodenum, compressing the duct of Santorini. The duct of Wirsung was occluded by two stones.

PATHOLOGY

The pathologic changes in pancreatitis are described from observations at autopsy and operation, and usually represent later phases of the process. Recent experimental evidence has demonstrated the earliest response of the pancreas to injury, namely edema. Hallenbeck, Jordan and Kelly[125] reported pallor, swelling and glassy induration within minutes after injecting bile into the ducts of dogs. Edema may develop in any part of the gland, most commonly the head. Smyth[117] noted congestion of the blood vessels shortly after induction of pancreatitis, with suppuration or enlargement of the adjacent lymph nodes. Microscopically, edematous fluid may be identified in the interstitial fluid. In addition to edema there is inflammatory cellular infiltration of the interstitial spaces, necrosis and disintegration of acinar cells, intrapancreatic and extrapancreatic fat necrosis and hemorrhage from necrotic blood vessels, as described by Grossman.[126]

Elman[47] has stated that resolution occurs in most cases without fibrosis. In a small group, edema progressed to necrosis or hemorrhage resulting in permanent damage. This progression is not predictable and cannot be explained, except that severe edema is more likely to precede it. Fat necrosis may be present even in mild cases of edematous pancreatitis. In view of the repeated finding of elevated blood amylase levels in patients suffering from acute abdominal pain in whom resolution is spontaneous, it may be inferred that these are cases of acute edematous pancreatitis with mild course.

Hemorrhage occurs as a result of necrosis of capillary or blood vessel walls. Fatal bleeding has been reported from the erosion of a medium sized vessel. The peritoneal fluid in acute hemorrhagic pancreatitis may be the color of "prune juice." Bleeding causes the ecchymosis that occasionally appears in the flank (Turner's sign) or around the umbilicus (Cullen's sign). These are due to blood coursing from the retroperitoneal area of the pancreas along the abdo-

minal wall becoming ultimately localized in one place.

Necrosis of the pancreas is seen in gray blackish areas which may liquefy and form cysts. Microscopically, the cells are pale, and disintegration of the acini, islet cells and connective tissue occurs. Areas of necrosis may be sharply demarcated from uninvolved pancreas by a band of inflammatory cells and a layer of red cells. Small necrotic areas are usually replaced by fibrosis. Larger areas may slough out and form cysts. Occasionally, pancreatic duct obstruction is observed with dilatation of the lumen and flattening of the mucosal lining. Inspissated secretions or metaplasia of the duct epithelium may produce obstruction.

Suppuration occurs rarely and is due to localization of bacteria. Small abscesses may be present. The ducts may be blocked by pus. A pseudocyst may become infected, producing an abscess.

Traumatic fat necrosis may occur in any fatty tissue, notably the breast, and is apparently due to the action on neutral fat of a lipase, but is most commonly seen in pancreatitis. Fat, released from the cell by injury, is changed to fatty acid and glycerol. Glycerol is water-soluble and is carried into the lymphatics. Fatty acids combine with calcium to produce soaps which do not leave the site of injury.

In most cases fat necroses are seen on the surface or within the gland in any area in which fat may be present. A whitish-yellow, hard nodule is present, surrounded by inflammatory areas. They may occur in the mesentery, the omentum or the retroperitoneal fat. The peritoneum may contain innumerable areas of fat necrosis, and the subpleural and pericardial fat may be involved. Perry[127] has shown that in pancreatic necrosis lipase travels along lymphatic pathways.

Microscopically, fat necrosis is recognized by the presence of injured cells, leukocytes, red cells, crystals of fatty acids and giant cells. Edmondson et al. have studied the question of the fate of the calcified areas of fat necrosis and concluded that these areas are not the sites of subsequent calcification.[128] The formation of inorganic calcium salts in the place of calcium soaps requires some mechanism, as yet unknown, for the rapid removal of fatty acids. Calcium stones, in their experience, are found only in the ducts of persons who have chronic pancreatitis as a result of long-standing obstruction, which results in precipitation of inorganic calcium salts.

Changes in the liver in acute hemorrhagic pancreatitis have been described. Fisher and McCloy[129] noted focal necrosis of the liver associated with bile stasis in some cases and more widespread changes with hemorrhage and cellular degeneration, together with dissociation of liver cell cords. Bile stasis and casts of inspissated bile were present. Pericholangitis, nuclear pleomorphism and mitotic activity in liver cells were seen. Schiller[130] has reported evidence of fat necrosis in the liver, ascribing it to the reflux of pancreatic juice into the biliary tree.

Fatty liver has been noted in dogs in association with acute pancreatitis. Groen[131] fed a diet consisting of only bacon fat to nine dogs over a long period. Death occurred within five to seven months. Four of five animals had acute pancreatic necrosis with severe fatty infiltration of the liver. Considering the mode of production of the two conditions, it is likely that the fatty liver was due to the diet rather than to the hemorrhagic pancreatitis.

Necrosis and perforation of the common bile duct have occurred in acute pancreatitis with bile peritonitis, as reported by Zaslow.[132] Presumably, the intrapancreatic and intraduodenal portions of the common bile duct are involved in the necrotic process within the pancreas.

Pleural effusion has been noted in acute pancreatitis by Lipp and Aaron,[133] and Weiner[134] described hemorrhagic pleural effusion in recurrent acute pancreatitis. Pericardial and pleural fat necroses have been described by Paxton and Payne.[37]

Renner[135] noted a lower nephron syndrome which terminated fatally in a patient in whom acute pancreatitis developed after prostatectomy, and he suggested that increased circulating trypsin might have caused these changes. They cited Mirsky and Freis[136] who have presented evidence indicating that proteolytic enzymes liberated from injured tissue may damage the kidney. Dehydration and shock with marked lowering of blood pressure are other factors to be considered in this connection.

Acute pancreatitis has been noted in an annular pancreas[137] and in a heterotopic pancreas.[138]

The mortality rate in acute pancreatitis is appreciable. Siler and Wulsin[250] studied the lethal factors in acute pancreatitis and could reach no definite conclusions. They suggest that increased blood enzyme concentrations may

cause circulatory collapse and damage to the kidney. Peripancreatic edema and hemorrhage may involve the mesentery, the periaortic tissues and the periadrenal and perirenal fat. Acute adrenal insufficiency may result.

CLINICAL PICTURE OF ACUTE PANCREATITIS

There is no characteristic picture of acute pancreatitis but a definite correlation exists between the severity of the process and the intensity of symptoms. The milder forms may occur in the form of digestive distress, pain and nausea, and the diagnosis may be made by demonstration of elevated blood enzymes of pancreatic origin when an alert observer suspects the presence of the disease. On the other hand, there may be a severe fulminating course with early death, the diagnosis being made at autopsy.

The initial symptom is pain, which is rarely if ever absent, beginning after a heavy meal[41] or alcoholic excess;[21] it may be unrelated to any specific incident. Pain begins in the epigastrium or the right hypochondrium and radiates to the back and left flank. After inserting electrodes into the pancreas of fifteen patients, Bliss et al.[139] concluded that pain originating in the head of the pancreas becomes localized in the mid-epigastrium and that pain stemming from the tail of the pancreas becomes localized in the left epigastrium. The pain is steady and severe, rarely intermittent. Frequently, just as in carcinoma of the pancreas, the pain is relieved by bending forward.

Nausea and vomiting occur frequently. Constipation is common, probably as a result of direct or reflex peritoneal irritation. Diarrhea is rare. Chills are infrequent and are the augury of a complicated course with abscess formation.

Fever is not usually high, ranging from 101° to 103°F.; high fever may presage a difficult course. Tachycardia is common. Blood pressure may be low in severe hemorrhagic pancreatitis and may be associated with cyanosis, tachycardia and signs of shock. These signs are of ominous prognostic significance.

Gastrointestinal bleeding has been seen in acute hemorrhagic pancreatitis. O'Brien and Thayer[140] noted the passage of bright red blood through the rectum in four patients and ascribed it to inflammation of gastrointestinal mucosa in contiguity with the inflamed pancreas.

Examination of the abdomen reveals tenderness, guarding and distention in most cases due to paralytic ileus and the chemical peritonitis. Occasionally a mass may be felt in the right or left upper quadrants of the abdomen due to early formation of pseudocysts containing debris, blood and fluid. Occasionally the mass may be due to an abscess or to an inflamed omentum which is the seat of fat necrosis. Examination of the chest may show congestion, atelectasis or pleural effusion at the left base.

Transient icterus is seen in about 25 per cent of cases. It may be due to obstruction of the common bile duct by gallstones or to edema of the head of the pancreas compressing the terminal portion of the common bile duct. Infrequently it may be due to hepatitis, a response of the liver to the same noxious agent which produced the pancreatitis (alcohol?) or to increased concentration of pancreatic enzymes reaching the liver by the portal vein.

The cutaneous manifestations of acute pancreatitis have been reviewed recently by Sigmund and Shelley.[141] The first reported changes were described as morbilliform lesions, and examination of the skin at autopsy showed subcutaneous fat necrosis. Cyanosis was reported by Halsted.[51] Turner[142] described bluish discoloration of the flanks (Grey-Turner sign) in association with a large collection of fluid in the peritoneum, which he ascribed to fat necrosis from pancreatic enzymes in the skin. Cullen[143] and Hofstätter[144] described a periumbilical discoloration in ectopic pregnancy, which may be reproduced by any condition in which bloody fluid is present in the abdomen. This is known as Cullen's sign. Both signs are due to the passage of hemorrhagic fluid through the peritoneal apertures and fascial planes, and the blood pigment then undergoes the changes seen in all ecchymoses. In acute pancreatitis these discolorations are seen three or four days after onset but Cullen's sign may be present within hours of the rupture of an ectopic pregnancy. Phelps and Lemmer[145] took a biopsy specimen of a Grey-Turner area and found moderate perivascular infiltrate. Zaaijer[146] reported subcutaneous fat necrosis in a similar area which he ascribed to the action of trypsin. Davis[147] reported cyanotic staining over the abdomen with petechial patches over the buttocks, a brownish discoloration just below the ribs posteriorly, and some mottling of the skin of the limbs.

Sigmund and Shelley[141] have observed livedo reticularis in a patient with acute pancreatitis,

an extensive area of cyanotic, marble-like reticulated discoloration of the abdominal wall. They credit Walzel[148] with having first described this sign in 1927 on the abdomen, chest and thighs. They consider the lesion to be due to circulating trypsin which has produced widespread intravascular damage and generalized skin change. A smaller indurated edematous area was also noted on the abdominal wall which the authors believe may be a local histamine release reaction to trypsin.

Review of Fifty-Eight Cases of Acute Pancreatitis. A survey of fifty-eight cases of acute pancreatitis treated at the Mount Sinai Hospital in the years 1940 to 1949 is of interest in depicting the features of the disease. In each case the diagnosis was corroborated by demonstration of hyperamylasemia or the presence of the disease at autopsy or operation.

Of the fifty-eight patients, twenty-nine were men and twenty-nine women. Twelve (21 per cent) were from ten to thirty-nine years old and forty-two (79 per cent) were above forty. The importance of acute pancreatitis as a disease of older age was illustrated by twenty patients who were in the seventh and eighth decades (34 per cent). Predisposing factors included the presence of disease of the gallbladder in thirty-two (55 per cent) and of alcoholism in eight (14 per cent), and of an operation (subtotal gastrectomy) in two (3.5 per cent). No significant factor was present in sixteen, or 27 per cent.

In fifty-three patients (90 per cent) the onset was acute with severe, sharp pain. In the remainder the symptoms seem to have developed slowly or to have been unrecognized. Pain was present in all patients, usually severe and located in the epigastrium and right upper quadrant of the abdomen in most (85 per cent), in the left upper quadrant of the abdomen in 5 per cent and the chest in 4 per cent. Nausea and vomiting were present in forty-four (76 per cent). Constipation occurred in fifty-seven (98 per cent). Chills were present in five (9 per cent) and presaged a serious course. Fever was present in all patients, varying between 100° and 105°F.; thirty-two (55 per cent) had fever between 101° and 103°F.

All patients were acutely ill. Tachycardia and rapid pulse were present in all. Cyanosis was seen in two and was of serious import. Jaundice was present in thirteen (22 per cent) at some time during the course, most commonly in those who subsequently had disease of the gallbladder (ten of thirty-two, or 33 per cent, had disease of the gallbladder).

Physical findings included tenderness and rigidity in the epigastrium and right upper quadrant of the abdomen. A mass was felt in only eight patients. A Gray-Turner sign was seen in two patients, Cullen's sign in one. Examination of the rectum yielded no diagnostic information.

The diagnosis was made in twenty of the fifty-eight cases on the basis of a rise in blood amylase ranging from 190 to 575 units. Ten patients had hyperglycemia; of these, eight were known to have diabetes. Hyperglycemia was found at some time or another in fifteen patients (25 per cent); albuminuria in twenty-seven (46 per cent). Serum calcium was not determined often enough, but one case terminating fatally showed a serum calcium of 7.1 mg per cent.

Moderate leukocytosis was present in 75 per cent (white blood count 10 to 20,000/cu. mm.) and was marked (20 to 30,000/cu. mm.), in 25 per cent of these cases. Elevation of the blood urea was a serious omen. Eight patients with blood urea values above 40 mg. per cent died. Bilirubin values in the patients with jaundice varied from 1.7 to 16 mg. per cent. Elevated serum alkaline phosphatase was found in six patients, ranging from 18 to 25 King-Armstrong units.

Roentgen studies were made of thirty-one cases. Nine showed no abnormality. Nine revealed dilated loops of small bowel, and two of these had large bowel dilatation. Nine showed gallstones by cholecystography. One patient was given a barium meal, and a filling defect was shown in the antrum; at operation, the stomach was shown to be free of disease. Of those patients in whom postoperative cholangiograms were taken, two showed normal bile ducts and one showed a normal duct and pancreatic reflux. Electrocardiograms showed myocardial disease in nine, and in no case did these observations resemble those reported in acute pancreatitis.

Twenty-four cases were of the edematous type, and twenty-four showed variable degrees of edema, necrosis and hemorrhage. Ten patients had abscesses in the pancreas. Twenty-five patients were treated medically, and ten died, a mortality rate of 40 per cent. Thirty-three patients were operated upon and nine died,

a surgical mortality rate of 27 per cent. The over-all mortality rate was 33 per cent.

The operations included cholecystostomy in eight, cholecystectomy in thirteen, cholecystectomy and common bile duct drainage in three, common bile duct drainage only in two, drainage of the lesser sac in one, biopsy specimen of the omentum obtained in six and exploration with no definitive procedure in three.

Of thirty-nine patients who survived, there were only two who progressed to syndromes suggesting chronic relapsing pancreatitis. Twelve could not be followed; of the remaining twenty-five, nine had serious symptoms for periods ranging from one to four years after the attacks.

Age Incidence of Acute Pancreatitis. Acute pancreatitis may occur at any age but is most common in middle and later life. Women seem to be affected more often than men, possibly due to the higher incidence of disease of the gallbladder. A survey of the extremes of age is of interest.

Shanks, Acton and Cottrell[149] reported acute pancreatitis in a ten year old girl who had a normal gallbladder. Dobbs[150] described a twelve year old girl operated upon for acute pancreatitis, and reviewed fourteen other cases. The age was from two to thirteen years. In six cases no definite cause could be found. Trauma preceded four cases. Ascaris was responsible for three, and one patient had disease of the gallbladder. He includes a discussion of 119 cases of mumps with pancreatitis; all recovered, two requiring operation.

Veghelyi[151] has described the picture of pancreatitis in children who had mumps, with sudden onset, high fever, vomiting and pain, and occasional jaundice with splenomegaly. Recovery occurs in four or five days. In children, the disease is most often seen in association with mumps.

Brush, Carlson and Zeller[152] studied the findings of thirty-one patients over sixty-five years of age who had acute pancreatitis, and made some interesting observations. Severe upper abdominal pain was the outstanding symptom. Shock was minimal, occurring in 10 per cent of the patients. Muscular spasm was minimal. Upper abdominal distention was moderate, and muscle guarding was present in only one-third of the patients. Jaundice was present in 45 per cent. The serum calcium was lowered in only one instance. Disease of the biliary tract was present in 74 per cent. Three deaths occurred in the 31 cases, one had severe diabetes, one had coronary artery disease and one had severe hemorrhagic necrosis with stone impacted in the common bile duct. These observations would suggest that acute pancreatitis is no more serious in the older age group than in any other age group. Siler and Wulsin[10] found, however, that in two-thirds of a group of twenty-two cases which terminated fatally, the patients were over age fifty-one.

LABORATORY DATA

Serum Enzymes in Acute Pancreatitis. The most valuable diagnostic finding in acute pancreatitis is the elevation of amylase in the blood. This enzyme originates within the pancreas; the salivary glands also elaborate and secrete it into the gastrointestinal tract. A pathway for the passage of amylase from the pancreas into the blood stream has been suggested by the experimental work of Popper and Necheles[153] who found that, with pancreatic trauma, blood amylase concentration in the pancreatic veins increased, while lymph amylase did not Howard, Smith and Pekes[154] demonstrated markedly increased enzyme values in the pancreatic veins after trauma. Tuchman, Schifrin and Antopol[155] produced a considerable rise in pancreatic enzymes of the serum of normal dogs (up to 1400 per cent) four hours after injection of mecholyl, and a minimal response was attained (0.0 to 66.0 per cent) in pancreatectomized dogs. The concentration in the pancreatic arteries was not elevated. Their results were advanced to support the thesis that the relevant blood enzyme values are increased by passage from the pancreas into the blood stream. In the normal pancreas, a small quantity of enzymes pass from the acinar cells through the interstitial spaces into the blood stream, representing some degree of endocrine secretion of an exocrine substance.[156] The evidence suggests that a rise in intraductal pressure accelerates the passage of enzymes into the blood. Secretin, which stimulates water and bicarbonate but not enzyme secretion, will cause a rise in serum enzymes in the presence of obstruction, as shown by Grossman[157] and Lopusniak.[158]

Serum amylase is best measured by the method of Somogyi,[159] a procedure which measures the quantity of glucose liberated by amylotic hydrolysis. In diabetes and in temporary hyperglycemic states, the method may not be accurate. Normal values range from 60

to 180 units (mg. glucose per 100 cc. serum). This test requires at least an hour for performance; many attempts have been made to develop a more rapid method. Fishman and Doubilet[160] have introduced a ten-minute test, based on a starch-iodine method, which has proved of value in their hands.

Serum amylase is elevated early in the course of acute pancreatitis. This elevation may be present for only a short time; hence normal amylase values do not imply absence of acute disease of the pancreas. Values as high as 8,000 units have been reported but most cases fall within the 200 to 800 range. In our own series, values ranged between 180 and 440 units. Normal values are reached ordinarily within two to three days. McCorkle and Goldman[161] have reported six different patterns in a group of forty-three cases of acute pancreatitis: (1) sharp rise and fall to normal; (2) sharp rise and fall to subnormal level; (3) fluctuation within the normal zone and slightly above and below the usual normal range; (4) sustained high values which may occur in extension or continuation of the disease; (5) secondary elevations several days after fall to normal levels, indicating exacerbations, and (6) slight elevations late in the disease in patients seen several days after onset.

Apparently no constant relationship exists between the severity of the disease and the height of the serum amylase values. Some of the milder forms may show marked elevations. During the most severe attacks, culminating in early death, blood enzyme values may be markedly decreased due to destruction of the pancreas or to the formation of a large pseudocyst in which all the enzymes are drained instead of passing into the blood stream.

Serum lipase, as measured by the method of Cherry and Crandall,[162] is a valuable diagnostic aid because it may be elevated after the serum amylase has returned to normal. Its usefulness is impaired by the fact that the test requires twenty-four hours for performance. Values above 1.0 ml. N/20 NaOH are considered significant by some, and above 1.5 ml. are considered significant by others.

Since blood contains antitryptase, trypsin cannot be measured satisfactorily. Innerfield et al.[163] have proposed the plasma antithrombin titer as a measure of blood trypsin and have found it to be elevated consistently in persons with acute pancreatitis, noting an average of 27.6 seconds for mean clotting time as compared with 16.4 seconds for normal man or patients with acute diseases other than pancreatitis. Fifty of 55 patients exhibited a high titer three to five days after onset of the disease at a time when the blood amylase values were of no help in corroborating the diagnosis. Others, notably Dreiling et al.,[164] have found no consistent relationship in acute pancreatitis.

Determination of the corresponding urinary enzymes is not employed often in view of the greater value of blood enzymes. However, urinary amylase may remain elevated after return of the serum amylase to normal levels. The normal values, according to Nothman who used[165] the saccharogenic method of Somogyi, are from 80 to 350 units per 100 ml. Urinary lipase determinations are rarely used. No satisfactory method exists for determining urinary trypsin.

Elevated Serum Enzymes in Conditions Other than Disease of the Pancreas. A variety of diseases, abdominal and extra-abdominal, may be accompanied by an elevation of the serum enzymes, and not infrequently a difficult diagnostic problem is presented. Hyperamylasemia is encountered in cases of ruptured peptic ulcer, as reported by Probstein et al.[177] in four of seventeen cases of perforated ulcer, and also in cases of penetration of posterior wall duodenal ulcers into the pancreas. Polowe[178] described elevations of serum amylase in (1) pneumonia, (2) perforation of peptic ulcer, (3) high intestinal obstruction, (4) salivary duct occlusion, suppuration or mumps, (5) uremia and (6) adrenal cortical insufficiency in the dog. Raffensperger[176] reviewed twenty-one cases of intra-abdominal disease with elevated serum enzymes in which no disease of the pancreas was present. Five patients had perforated peptic ulcers. Four had partial small bowel obstruction. Eight had acute peritonitis secondary to abnormalities in other organs. One was a child with a strangulated diaphragmatic hernia, and three had uremia from intrinsic disease of the kidney.

Guszich[179] found elevation of serum lipase in the postoperative course of eleven of sixteen patients after cholecystectomy and in seven of eight after gastrectomy; he ascribed these findings to manipulation of the head of the pancreas. Fifty per cent of abdominal operations in which the pancreas was not touched were followed by elevation of serum lipase. Guszich had no adequate explanation. It is

possible that spasm of the ampullary structures secondary to starvation, morphine and sedatives may have initiated obstruction of the flow of pancreatic juice. Meyer and Amtman[180] found elevations of urinary amylase in patients who had peptic ulcer penetrating into the pancreas.

Malinowski reported hyperamylasemia following administration of demerol.®[181] Nossel and Efron[182] obtained a marked increase in serum amylase in forty-three patients after injection of morphine, presumably due to the constrictor effect of morphine on the bile ducts. Alcohol did not increase serum enzyme values. Bennett and Burgess[183] described markedly elevated serum amylase in a patient who took 0.75 gm. of morphine intravenously in an attempted suicide. A plausible explanation lies in the spasmogenic properties of these drugs which may lead to obstruction of the pancreatic ducts. Elevations of serum lipase occur in persons with carcinoma of the pancreas, obstructive jaundice due to stone, tumors and cirrhosis of the liver, viral hepatitis, intestinal obstruction and peritonitis, as noted by Machella.[184] Weiss et al.[185] have reported, as an incidental observation, elevated serum amylase in a patient with bronchogenic carcinoma.

Changes in the Blood. The leukocyte count is constantly elevated, ranging from 10,000 to 30,000. Herfort[166] noted a decrease in lymphocytes as a regular finding in thirty-eight patients with acute pancreatic necrosis. The degree of lymphopenia paralleled the severity of the pancreatitis, and clinical recovery was accompanied by moderate lymphocytosis. The erythrocyte count is not usually lowered but significant, progressively developing anemia may indicate hemorrhage into the peritoneal cavity.

Elevation of blood urea nitrogen is not uncommon in the more severe cases. Shingleton, Anlyan and Hart[167] have noted changes in blood coagulability. Small amounts of trypsin *in vivo* will promote coagulation of blood by conversion of prothrombin to thrombin. Larger amounts prolong the clotting time due to consumption of prothrombin and fibrinogen secondary to massive intravascular clotting.

Glycosuria occurs in about 11 per cent of all patients with acute pancreatitis, according to Shumacker.[168] Involvement of the islets of Langerhans, with insulin deficiency, is presumed to be the cause. With resolution of acute pancreatitis the glycosuria disappears. Most observers feel that glycosuria persisting after the acute attack is indicative of a severe inflammatory and necrotic process. Transient hyperglycemia may be found more frequently than glycosuria. Brocq and Varangot[169] found blood sugar levels over 150 mg. per 100 ml. in fifty-seven of seventy-two patients with acute pancreatitis. Bernhard[170] stated that alterations in the glucose tolerance curve are more common than either glycosuria or hyperglycemia, and he suggested that this test be performed more often. Warren, Fallis and Barron[171] suspect that diabetes is not rare in persons with acute pancreatitis, having found five cases of diabetes in thirty-eight patients with severe acute pancreatitis. When undetected diabetes complicates pancreatitis, the mortality rate is very high.

Hypoprothrombinemia, positive cephalin flocculation reactions and thymol turbidity tests have been noted. Elevation of serum alkaline phosphatase may reflect biliary obstruction but may also be the result of pancreatic ductal block and increase of pancreatic alkaline phosphatase.[172]

Diagnostic tap of the peritoneum may be valuable in acute pancreatitis. Keith, Zollinger and McCleery[173] have reported fifteen cases in which a diagnostic tap was done. The procedure was performed under local anesthesia in the left lower quadrant of the abdomen. In three instances no fluid was obtained. In twelve cases the peritoneal fluid amylase was much higher than that of the blood and remained elevated for two or three days after the blood amylase had fallen to non-diagnostic levels. Values varying from 400 to 1600 units were reported. The presence of amylase in the peritoneal fluid is due to transudation into the peripancreatic tissues and the peritoneal cavity. Turbid yellow fluid is present in interstitial or edematous pancreatitis, a reddish-brown fluid in the hemorrhagic type; occasionally, gross and microscopic fat globules may be seen.

Changes in the Urine. Albuminuria is present in about 25 per cent of cases and is usually transient. As already mentioned, glycosuria occurs in about 11 per cent of all patients.[168] The development of hyperglycemia and glycosuria in persons with acute pancreatitis has not been adequately explained. Considerable destruction of islet cells must occur before insulin formation is so impaired as to result in defects in carbohydrate metabolism. The transitory nature of these defects suggests that the alpha

cells of the islets may be stimulated, with overproduction of glucagon, the hyperglycemic factor.[174] Marked suppression of urine may develop in those patients with acute pancreatitis[135] in whom a lower nephron syndrome develops.

The Secretin Test in Acute Pancreatitis. The response of the pancreas to the secretin test following acute pancreatitis has been studied by Dreiling[175] in forty-eight patients. The volume, bicarbonate and amylase concentration of the pancreatic secretion were diminished slightly in twenty patients and were normal in the majority of patients within the first week of illness. When abnormal secretion is found, it has no definite characteristics which aid in diagnosis. A test giving negative results is of no significance because pancreatic function may have returned to normal by the time the test is performed. Positive reactions are of great importance, indicating persistence of pancreatic damage and the possibility of development of chronic pancreatitis.

Electrolyte Disturbances in Acute Pancreatitis. Edmondson and Fields[186] observed the occurrence of low serum calcium values in persons with acute pancreatitis, and Edmondson and Berne[187] emphasized the significance of hypocalcemia in this connection. In their opinion, hypocalcemia is due to the rapid mobilization of calcium from the blood stream into the areas of fat necrosis for saponification of the liberated fatty acids to form the corresponding calcium salts. Low values (below 7 mg. per 100 ml.) were of serious prognostic omen and frequently were associated with tetany. Postmortem analysis in one case revealed an estimated 1,500 mg. of calcium in the pancreas. Another reason given for the low serum calcium is that excessive stimulation of the adrenals by ACTH may promote calcium excretion into the bowel.

Hayes[188] has studied calcium metabolism in acute pancreatitis. He found depression of serum calcium in most patients between the second and fifteenth days of the disease, the lowest level occurring on the sixth day, and noted a correlation between the clinical severity of the disease and the degree of depression of serum calcium. Tetany occurred in two patients in whom the serum calcium levels were normal. Hayes postulates that the ionized calcium is decreased due to the increased level of fatty acids in the serum associated with elevation in serum lipase. Since ionic calcium is bound by fatty acids, tetany may not respond to calcium administration, and parathyroid hormone may be given to increase the ionic calcium. Lipp and Hubbard[189] studied the calcium level in nine patients with acute pancreatitis. Depression of calcium occurred in all between the third and fourteenth days of the disease.

Edmondson, Berne, Homann and Westman[190] have noted hypokalemia in nineteen of twenty-seven patients who had acute pancreatitis. Alkalosis, intravenous saline solution, nasogastric suction and increased production of ACTH are considered to have played a part in producing the low serum potassium. The breakdown of body protoplasm can account for mobilization of potassium into the blood and excretion in the urine. Hyperpotassemia was noted in five fatal cases secondary to tissue breakdown and secondary renal failure. Low magnesium levels were noted in four patients in the first five days and lasted twenty-four to forty-eight hours. No correlation was noted between hypomagnesemia and low serum calcium or potassium. Carbon dioxide values were not appreciably changed. Low sodium values were found in eight patients, and no correlation was noted with the severity of the disease or with the changes in other electrolytes.

Electrocardiographic Changes in Acute Pancreatitis. In 1943 Gottesman, Casten and Beller[191] described changes in the electrocardiograms of five patients with acute pancreatitis simulating those of coronary occlusion. These findings were present at the height of the disease, as were elevated serum amylase values. As the patients improved and the hyperamylasemia reverted to normal, the electrocardiographic changes disappeared. These changes consisted of depression of the S-T segment in leads II and III, and the presence of diphasic T waves in leads I, II and III. At autopsy in one patient they found 50 cc. of reddish brown fluid in the pericardium, slight dilatation of the left ventricle, but no evidence of coronary occlusion or myocardial infarction was present. The same workers[192] produced extensive electrocardiographic changes in experimental hemorrhagic pancreatitis in dogs. Bockus[193] has described electrocardiographic changes in three patients. Dittler and McGavack[194] described a patient who had acute pancreatitis and showed electrocardiographic evidence of myocardial infarction with severe disturbances of rhythm, in whom the autopsy revealed normal coronary arteries and myocardium. Bauerlein and Stobbe[195] reported a similar case in which extensive electrocardio-

graphic changes were noted. The autopsy showed no abnormalities of the coronary arteries or of the endocardum or myocardium. The cause of these abnormalities is not apparent. They may be due to coronary insufficiency secondary to a shock-like state but they are not seen in persons with other acute abdominal emergencies. Bockus[193] has suggested that a low potassium concentration may be responsible. Bauerlein and Stobbe[195] suggest that fat necrosis in the myocardium or some remote chemical effect of massive fat necrosis may be responsible. The importance of the electrocardiographic changes lies in the need for differentiation of coronary thrombosis from acute pancreatitis.

Siler and Wulsin[10] have been unable to find a consistent electrocardiographic pattern in acute pancreatitis but advance two hypotheses as to mechanisms involved: (1) a low serum calcium level and (2) a disturbance of the vagal impulses via the celiac plexus.

Radiologic Findings in Acute Pancreatitis. The pancreas cannot be demonstrated by direct radiologic means. Its density is only slightly different from the peripancreatic structures and no contrast medium has been developed which will outline the contours of the organ or its ducts. Direct visualization is possible in instances in which the pancreas has undergone extensive pathologic changes, such as calcification within the ducts or in the presence of a cyst. The vast majority of cases of acute pancreatitis do not show calcification, and specific radiologic diagnosis must depend on other means.

Bronner[196] was the first to suggest the barium swallow in acute pancreatitis in order to demonstrate the relation of the pancreas to the stomach and duodenum. Indirect evidence of enlargement of the head or body was deduced from displacement of the stomach and duodenum. Case[197] advised a preliminary film, to include the diaphragm and pulmonary bases. He noted limitation of excursion of the left diaphragm, pleural exudates on the left side, ill defined left psoas muscle contour, abnormal gaseous distention of the colon, and paralytic ileus. Gallstones have been seen in many cases. Goldmann[198] has described a somewhat indistinct shadow in the region of the pancreas of the same density as the liver which was set off by the gas-distended stomach above the transverse colon below. The absence of free air under the diaphragm may help to differentiate acute pancreatitis from perforated peptic ulcer.

Administration of barium is not advisable in acutely ill patients but when it has been given, certain other observations have been reported, such as elevation of the stomach, enlargement of the duodenal loop, collection and stasis of appreciable quantities of barium in the dependent portions of the duodenum, and a defect in the region of the duodenojejunal flexure.

Metheny, Roberts and Stranahan[199] have commented on the frequent occurrence of the presence of a gas bubble in the atonic duodenal bulb. Glenn and Baylin[200] have described persistent spasm of the duodenal loop with changes in contour. Areas of spasm in the transverse colon, the splenic flexure and the ileocecal area have been noted, probably due to fat necrosis in the area. They also comment on the finding and significance of duodenal diverticulum in an occasional case of acute pancreatitis.

Grollman, Goodman and Fine[201] have described eight patients with acute pancreatitis in whom an isolated, distended loop of small intestine has been seen, often in the left upper quadrant of the abdomen but occasionally in other regions of the abdomen. A similar loop has been described by Levitan[202] in persons with acute appendicitis and acute cholecystitis as the "sentinel loop."

Radiologic interest has recently been directed towards visualization of the gallbladder in persons with acute pancreatitis. Kaden, Howard and Doubleday[203] subjected to this procedure twenty-three patients with acute pancreatitis in whom disease of the gallbladder was subsequently ruled out, either by operation or cholecystography. Visualization did not occur or was poor in fifteen. Silvani and McCorkle[204] found non-visualization of the gallbladder in sixteen of twenty-eight patients. These authors were not able to explain this phenomenon but emphasize its importance in order to prevent unnecessary cholecystectomies in persons with pancreatitis. Radakovich et al.,[205] on the basis of experimental work, have suggested that obstruction to the pancreatic duct prevents absorption of cholecystographic media. Howard found non-visualization after battle injury. Kaden et al.[203] suggest that a paralytic ileus prevents absorption of the dye. It is possible that edema and spasm of the biliary sphincteric mechanisms prevent filling of the gallbladder.

Poppel[206] has summarized the x-ray findings in acute exacerbations of relapsing pancreatitis.

In addition to those described by previous observers, he has included the demonstration of an enlarged edematous papilla of Vater and marked irritability of the stomach and duodenum. A subphrenic collection in the right and left subdiaphragmatic areas has been noted. Localized space-occupying lesions may be present in the retroperitoneal area behind the pancreas, in the lesser omentum between the stomach and liver, in the lesser peritoneal sac and in the gastrocolic ligament.

Evidence of varying amounts of fluid in the peritoneal cavity is given by a density throughout the abdomen and absence of normal organ outlines due to the loss of surrounding contrasting fat. The properitoneal fat layer may disappear. The outline of the left kidney may be obscured. Poppel[206] describes irregular, rounded, mottled areas of increased density scattered throughout the abdomen, which at operation and autopsy were found to represent fat necrosis without calcification. He also noted linear focal atelectases in the lungs (Fleishner lines).

DIFFERENTIAL DIAGNOSIS OF ACUTE PANCREATITIS

The diagnosis of acute pancreatitis should be established as quickly as clinical and laboratory facilities permit. A consideration of all the features which have already been discussed should lead to an accurate diagnosis. However, the difficulty of diagnosis is enhanced by the large number of acute abdominal emergencies which are well known to the clinician.

Biliary colic may resemble acute pancreatitis by virtue of pressure changes in the biliary circuit and associated inflammation of the gallbladder. Pain, tenderness and rigidity are frequently localized in the right upper quadrant of the abdomen. Stones in the common duct are frequently associated with chills, fever and jaundice. An elevated serum amylase is seen in about 20 per cent of cases of common duct stone, and differentiation may not be possible early in the course. Watchful waiting may be necessary before clarification.

Acute cholecystitis may be present with the same symptoms as pancreatitis. The pain is usually in the right upper part of the abdomen and may radiate to the right scapula. Marked tenderness and guarding are present in the right upper quadrant of the abdomen and in many instances a globular mass may be felt. Despite the severity of pain, the cholecystitis patient does not look as sick as the patient with pancreatitis.

Perforated peptic ulcer may resemble acute pancreatitis more than any other abdominal condition. Often, a history of ulcer may be elicited, although occasionally perforation may be the first indication of ulcer. Board-like rigidity is very often present in perforation. Plain films of the abdomen may show free air under the diaphragm. Although elevation of blood amylase may accompany perforation, the values are rarely as high as those attained in persons with pancreatitis.

Acute appendicitis, involving a retrocecal appendix in contact with the psoas muscle, and in relation to the gallbladder may require differentiation. Blood amylase levels are not usually affected.

Acute intestinal obstruction may cause difficulty in diagnosis, especially in view of the occasional hyperamylasemia. Cramp-like pain is associated with generalized abdominal distention. Vomiting, especially of fecal contents, is more common. Marked rigidity is not prominent. Visible peristalsis may be present. In mechanical ileus, auscultation will reveal high pitched notes, succussion splashes and peristaltic rushes. In pancreatitis the adynamic ileus is associated with distention and lack of peristalsis. The finding of a hernia, previous operative scar or abdominal mass will be of value. The roentgenographic picture may help but may not be of diagnostic significance.

Mesenteric thrombosis may present itself as intestinal obstruction with a less acute onset. It may be associated with slight bloody diarrhea which is rare in acute pancreatitis. Shock is more acute than in most cases of acute pancreatitis, and diffuse tenderness and rigidity are common. Roentgenograms may show a large dilated loop of bowel, the seat of infarction.

Dissecting aortic aneurysm will present with severe pain and shock. Absent pulsations may be noted in the femoral arteries with lowered blood pressure in the legs. The systemic blood pressure in the upper extremities may be elevated. A pulsating mass may be felt.

Kidney stone, especially on the left side, may simulate acute pancreatitis by virtue of left-sided pain and spasm. Hematuria and a flat film of the abdomen which demonstrates a stone may help in differentiation.

Acute coronary thrombosis with signs in the upper abdomen and symptoms such as that of

epigastric tenderness, pain and vomiting may be differentiated by electrocardiograms that persistently reveal characteristic abnormalities and the lack of elevation of blood enzymes of pancreatic origin.

Acute porphyria may simulate acute pancreatitis. The abdominal pain is usually severe and colicky. A history of vomiting at intervals and of increasing constipation is frequently elicited. Diagnosis depends upon the demonstration of porphobilinogen or abnormal porphyrins in the urine by the Watson-Schwartz test and by spectroscopic examination of the urine.

Acute lupus erythematosus may present an abdominal picture requiring differentiation from acute pancreatitis. Pleural effusion may be present in both diseases. The demonstration of lupus erythematosus cells in the peripheral blood or on bone marrow aspiration will help to differentiate the two.

Benign paroxymal peritonitis must be differentiated from pancreatitis. The disease begins early in life and attacks continue for many years. It is characterized by abdominal pain, constipation, leukocytosis and vomiting. Chest pain, worse on inspiration, is common. No elevations of blood amylase have been reported.

TREATMENT OF ACUTE PANCREATITIS

One of the major problems in the management of acute pancreatitis has been the question of surgical versus medical treatment. With advancements in knowledge of the pathologic physiology of the disease and the marshalling of newer specific measures in the handling of the abnormalities, the medical or conservative treatment has yielded more satisfactory results. The consensus of most observers is that surgery should be reserved only for specific situations, usually arising later in the course.

The first appraisal of the patient will not always predict the severity of the course, and one can never be certain when only edematous pancreatitis is present and when hemorrhage and necrosis will develop. The initial plan of treatment is usually the same in either case but each patient requires constant observation because of the severity of symptoms and the possibility of sudden dramatic change in the course.

Treatment is directed toward resolution of the pathologic process and includes (1) relief of pain, (2) treatment of shock and of associated fluid and electrolyte disturbances, (3) temporary inhibition of pancreatic secretion, (4) prevention of infection and peritonitis, (5) management of surgical sequelae, and (6) prevention of recurrences.

The severe pain of acute pancreatitis requires immediate relief. Morphine should not be used because, despite its analgesic action, it may produce duodenal spasm, spasm of the biliary and pancreatic ducts and of the sphincter of Oddi, thus aggravating the pathogenetic factors. Demerol® (meperidine hydrochloride) in doses of 100 to 150 mg. every four hours will relieve pain in most instances without appreciable spasmogenic effects. However, demerol possesses the property of inducing spasm of the sphincter and has been known to produce biliary colic.

Nitrites inhaled as amyl nitrite pearls, or in the form of 0.6 mg. of nitroglycerine (1/200 gr.) sublingually,[207] have been advocated to produce relaxation of the smooth muscle of the ducts and duodenum, but their effects are short and unpredictable and their hypotensive action may aggravate the shock of the disease.

Another drug which may relieve pain and induce hypotensive effects is tetraethyl ammonium chloride, as pointed out by Hyman and Burton.[208] The effects are attributed to blocking of sympathetic and parasympathetic impulses at the ganglionic synapse.[209] Berk[210] advocates the use of 1 to 5 cc. of 10 per cent solution of tetraethyl ammonium chloride intravenously every four hours. The dosage will vary with the tolerance of the patient and the degree of relief from pain. Intravenous aminophylline, advocated by de Alvare[211] in doses of 250 to 500 mg., may also contribute to muscle relaxation but the effect is short and hypotension may be aggravated.

Banthine® (methantheline bromide) has been used to relieve pain in acute pancreatitis. The beneficial quality may be its ganglionic blocking effect but it is more likely due to suppression of gastric and pancreatic secretion, and to its relaxant effect on the musculature of the upper intestinal tract and on the biliary and pancreatic ducts, as shown by Annis and Hallenbeck,[212] Howard, Evans and James,[213] Shingleton and Anlyan,[214] and Thistlethwaite.[215] The drug should be administered in a slow intravenous drip in doses of 100 mg. every six hours. Pro-banthine® (propantheline bromide) has a

similar effect and is administered in 15 to 30 mg. doses every six hours.[216]

Hexamethonium bromide (bistrium®) has been used by Davies, Moore and Wynn-Williams[217] in doses of 250 mg. by Levin tube every twelve hours, with unpredictable response. However, slow intravenous administration of 25 to 50 mg. in fractional amounts has some value.

Procaine hydrochloride has been given intravenously with success by Longo and Sosa Gallardo.[218] They advise 10 to 20 cc. of 1 per cent procaine hydrochloride at the rate of 1 cc. in 20 to 30 seconds repeated every three to four hours. In addition to the anesthetic, analgesic and antihistaminic action of procaine, it has a vasodilator effect and produces relaxation of the smooth muscle. All of these properties may help in the restitution of some of the pathologic effects in acute pancreatitis. Kyrle[219] has also used a local anesthetic, (panthesine) and Erlsbacher and Geisberger[220] have employed intravenous buscopan.

Paravertebral sympathetic and splanchnic nerve block has been used by Gage and Gillespie[221] for the pain of pancreatitis. One per cent procaine hydrochloride is injected into the paravertebral areas on both sides in the fifth to twelfth thoracic interspaces. Unilateral and bilateral splanchnic nerve blocks require administration of 1 per cent procaine hydrochloride into the loose areolar tissue anterior to the body of the first lumbar vertebra. These procedures may give relief by interference with pain transmission by visceral afferent fibers from the pancreas and by vasomotor and secretory changes in the pancreas.

Fractional epidural block has been used by Berk and Krumperman[222] with satisfactory results. A 10 to 20 cc. solution of 1 per cent procaine hydrochloride and cobefrin hydrochloride in 1:40,000 dilution is injected every twelve to twenty-four hours into the epidural space through an indwelling catheter. These workers have not obtained uniformly good results and suggest that fractional epidural block, if employed, should be used in conjunction with other measures.

Shock and electrolyte disturbances in acute pancreatitis are the results of vomiting, hemorrhage, necrosis and passage of toxic fluids into the abdomen. Transfusions of whole blood and plasma, and fluid infusions, are required to restore blood volume. Glucose in distilled water or saline solution must be administered carefully because of the disturbance in carbohydrate metabolism in pancreatitis. There seems to be no evidence that pancreatic secretion is influenced by hyperglycemia, as shown by Crider and Thomas.[223] If elevations of blood sugar are encountered, insulin should be given cautiously, since hypoglycemia is a powerful stimulus to the vagus.

Zollinger, Keith and Ellison[224] and Kenwell and Wels[225] advise administration of 100 to 200 cc. of 25 per cent normal human serum albumin solution for its effect in replacing the blood volume and for its antitryptic properties. Elliott, Zollinger, Moore and Ellison[226] treated five patients who had acute pancreatitis with daily infusions of 200 cc. of human serum albumin up to 800 to 1,200 cc. These patients showed deficits in circulating blood volume with loss of both plasma and red cell mass. All of the commonly accepted treatments were included in addition to the serum albumin. All patients recovered, only one suffering a mild attack of pulmonary edema. The improvement followed the same pattern observed in dogs which were treated with serum albumin for experimentally induced pancreatitis. Circulating plasma volume increased with a drop in antifibrinolysin titer. These investigators conclude that the major effect is from support of plasma volume and that definite benefit from trypsin inhibition during pancreatitis could not be established.

Jones[216] has used levarterenoe (levophed®) bitartrate for vascular collapse. Hydrocortisone (cortef) has been used in 100 mg. doses intravenously every six hours in desperately ill patients by Stephenson, Pfeffer and Saypol[227] and gratifying results were achieved. Bloodworth and Cohen[228] administered 100 mg. of cortisone intramuscularly as a first dose in a critically ill soldier, followed by 50 mg. every six hours for four days, which resulted in dramatic relief. Eskwith et al.[229] treated a case of acute hemorrhagic pancreatitis with 300 mg. cortisone daily for several days with gratifying results.

The hypocalcemia of acute pancreatitis may require 10 to 20 cc. of 10 per cent calcium gluconate intravenously twice daily. Calcium exerts a sedative effect on smooth muscle and may act to relieve pain. The low sodium, potassium and chloride concentrations may be corrected by giving lactated Ringer's solution and Darrow's solution.

Pancreatic secretion is suppressed by continuous nasogastric suction and the withholding of all fluids. By preventing the passage of hydrochloric acid and food into the duodenum, secretin formation is lessened, the secretory stimulus to the pancreas is minimized and the damaged gland is "splinted."

The various drugs, banthine, probanthine, tetraethylammonium chloride and hexamethonium, used for pain relief exert an inhibiting effect on pancreatic secretion. In addition, 0.6 mg. of atropine and 100 mg. of phenobarbital (subcutaneously) administered every six hours act to depress secretin, as does ephedrine sulphate when 25 to 50 mg. are administered subcutaneously every six hours.

Good effects have been reported from the use of radiation by Heacock and Cara.[230] Rauch and Stenstrom[231] have shown diminution in pancreatic secretin in a dog after radiation of the pancreas. However, this treatment is not extensively used.[232]

All patients with acute pancreatitis deserve early and adequate treatment against infection. Experimental evidence has accumulated which indicates the protective effect of antibiotics. Lewis and Wangensteen[233] have shown that experimental pancreatitis in untreated dogs resulted in death within twenty-four to forty-eight hours. In animals treated with penicillin and streptomycin the survival rate varied from 42 to 50 per cent. Persky et al.[234] have shown that aureomycin given orally for several days before or after production of acute hemorrhagic pancreatitis in dogs resulted in a survival rate of 100 per cent, while intravenous aureomycin or parenteral penicillin gave protection to the extent of a survival rate of 40 per cent. They suggested that the greater effectiveness of the oral route indicated that intestinal organisms are the major source of pathogens causing a lethal outcome in dogs. The Levin tube used in nasogastric suction offers an excellent avenue for administration of 0.5 gm. of aureomycin or oxytetracycline every six hours at times when suction is temporarily stopped. Either drug may be given in doses of 0.5 gm. every twelve hours. Penicillin should be given intramuscularly (600,000 units twice daily).

To combat abnormal tryptic activity that may favor progressive necrosis, trypsin inhibitor present in soybeans has been shown to be of value in dogs by Gillespie et al.[235] Its value in man remains to be proved. Rush and Clifton[236] have used soybean trypsin inhibitor, prepared by the method of Kunitz,[237] in experimental pancreatitis. They concluded that it counteracted the elevated proteolytic activity and shock.

Surgical Measures. In 1927 Schmieden and Sebening[38] compiled a total of 1,278 cases of acute pancreatitis in patients who were treated surgically in which the mortality rate was 51.2 per cent. DeTakats and MacKenzie[238] in 1932 were among the first to suggest that persons with acute pancreatitis should not be treated surgically. Only eight of twenty-two of their patients who were not operated upon died, a mortality rate of 36.6 per cent. Mikkelsen[239] treated thirty-nine patients with acute pancreatitis conservatively, which resulted in a mortality rate of 7.5 per cent. Demel[240] surveyed a large group of patients operated upon in the early stages and reported a mortality rate of 52 to 78 per cent. Machella[241] found a mortality rate of 35 per cent in 410 patients on whom surgery had been performed and a mortality rate of 20 per cent in a series of 354 conservatively managed patients. He concluded that a minimum mortality rate of 10 per cent must be expected in any series of cases, regardless of the therapy.

Baker and Boles[242] state that in the acute phase of pancreatitis early laparotomy is indicated in two situations, namely, (1) if the diagnosis is doubtful and (2) if biliary obstruction is present with jaundice. Rhoads, Howard and Moss[243] believe that all patients should be operated upon whenever possible for the following reasons: (1) decompression of the biliary tract reduces the probability of reflux of bile into the pancreas; (2) acute biliary complications are discovered and treated; (3) enzyme elevations do not make it possible to distinguish between primary pancreatitis and pancreatitis secondary to disease of adjacent organs; (4) operation permits drainage of infected areas, and (5) cholangiography can be done postoperatively.

The best argument against surgical intervention is the failure of surgeons to agree on any specific procedure. Early drainage of the lesser omental sac and the flanks may seem advisable but does not drain the seat of trouble, the pancreas. Drainage of the biliary tract may act to decompress the biliary pancreatic circuit.

Some believe that, since a necrotic pancreas tends to perforate into the lesser peritoneal

cavity, this area should be drained early through the foramen of Winslow. Bowers[244] has recently summarized current thinking on the use of surgery for persons who have acute pancreatitis. He believes that acute pancreatitis is of surgical interest only because of its similarity to other surgical conditions, which if not operated upon will go on to severe morbidity and mortality. These include perforated peptic ulcer, acute intestinal obstruction, acute cholecystitis, mesenteric thrombosis and perforated diverticulitis. If the surgeon finds acute pancreatitis he "should do as little as possible and get out quickly." If gallstones and common duct stones are present, and the procedure is feasible, cholecystostomy or cholecystectomy, with or without common duct stone removal and drainage, is advisable. Once the surgical episode is complete, the patient should be treated medically. Siler and Wulsin[10] believe that so much difference of opinion exists about surgery of the biliary tract that it is best to wait for the acute process to subside and to evaluate the patient's biliary status before deciding on operation.

On the other hand, Doubilet and Mulholland[245] advocate a much more aggressive approach. While agreeing with conservative treatment during the early period of the acute attack, they advocate exploration in the third week after onset. At this time pancreatic inflammation has subsided and the gallbladder and common duct may be explored. More recently, the same authors[246] have reported on the treatment of 319 cases of recurring acute pancreatitis by sphincterotomy and cholecystectomy. The operative mortality rate was 5.3 per cent and the recurrent morbidity rate 10 per cent in patients followed for two years. Blatherwick and Pattison[247] have described three cases in whom sphincterotomy was performed for recurrent pancreatitis. In all, acute hemorrhagic pancreatitis developed and the outcome, which was fatal, was attributed to extensive trauma to the head of the pancreas. Their experience induces them to advise extreme caution in the use of this procedure.

The immediate sequelae of acute pancreatitis, abscess and pseudocyst, may require drainage.

The management of the patient after the acute attack should be directed toward the prevention of future attacks. Toward this end Richman and Colp[248] have formulated a regimen paralleling the principles of treatment in persons with acute pancreatitis which includes a low fat diet, small frequent meals to minimize pancreatic secretion and avoidance of alcohol and spicy foods. Anticholinergic and antianalgesic drugs to minimize secretion and pain are used in addition to substitution therapy of pancreatin and insulin, if deficiency of the acinar and islet cells is demonstrated.

The subsequent care of the patient who has recovered from acute pancreatitis involves avoidance of predisposing factors. Overeating, obesity and alcoholic abuse seem to be the most important precipitating factors and should be interdicted. The vast majority of patients make a more or less complete recovery.

SUBSEQUENT HISTORY OF PATIENTS WITH ACUTE PANCREATITIS

Raker and Bartlett[249] studied 118 patients who survived an attack of pancreatitis. Forty-two patients had had no definitive treatment; of these, ten could not be followed for at least one year. Of thirty-two who were traced, twenty-two were asymptomatic, four had mild symptoms and six had recurrent symptoms. Fifty-nine patients had had cholecystectomy and common duct drainage; of these eight were not traced. The results were good in forty-seven of the remainder, fair in two and poor in two. Two had repeated attacks. Thirteen patients had had miscellaneous procedures—nine had had cholecystectomy and four common bile duct drainage. They concluded that in only a few patients did chronic relapsing pancreatitis develop and that biliary tract surgery should be done in those with disease of the gallbladder, since this may prevent recurrent pancreatitis.

Bockus et al.[19] reviewed a series of seventy-eight patients with acute pancreatitis. Thirty-six were of biliary tract origin, in thirty-one there was a significant history of alcoholism. They concluded that the alcoholic had more severe disease and a higher incidence of complications and recurrences. Pancreatic calcification appeared six times more frequently in the group of alcoholic subjects, and chronic relapsing pancreatitis occurred in most instances in this group.

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Clinic on Psychosomatic Problems

Long-term Psychotherapy in a Patient with Epigastric Pain

These cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric Service of the Massachusetts General Hospital under the direction of Dr. Erich Lindemann. This conference was edited by Dr. P. E. Sifneos.

Dr. Peter E. Sifneos: The patient, a twenty year old office clerk, has been followed up for almost five years. Treatment did not last more than a year and four months, but follow-up studies continued for three years and were probably more important than the treatment itself. The information gathered in the first three interviews shall be presented as if it were part of our psychiatric clinic intake procedure.

This information will include the relation of psychologic factors to the patient's medical symptoms, emotional development, personality, relationships with other people, ability to work, family and past history, and the impression made by the patient on one or more members of the intake team who interviewed him.

I wish that you would imagine yourselves members of the intake team; express your opinion about the nature of the problem and the diagnosis, as well as ideas about the kind of treatment which should have been offered to such a patient. The course of treatment and the outcome shall then be presented in detail.

The patient was referred by the Medical Clinic of this hospital in June, 1950. He complained of epigastric pain, nausea, vomiting, tremulousness and feelings of insecurity and anxiety. He had lost twenty pounds in weight during three or four months. His symptoms had begun when he was nineteen years old, at a National Guard Camp, in association with getting injections and blood tests during a physical examination. His apprehension was so great that the blood tests were postponed. This was about the time of the beginning of the Korean War. The symptoms got worse approximately four months before he came to the clinic.

Physical examination in the Medical Clinic was normal. Gastrointestinal series, urine examination, white and red cell blood count and blood smear were within normal limits. The patient was then referred to the Psychiatric Clinic.

He was seen first by Dr. Franklin Carter who believed that the patient had anxiety neurosis and could be helped by psychotherapy. Four or five weeks later the patient was assigned to a medical student, who saw him four times. Besides medical problems, the patient described fears of "needles, doctors and dentists." He mentioned feelings of insecurity, particularly in reference to his father and uncle. He thought his father considered him a coward, "a no good nut." His father was a Captain in the Navy and to have his only son a "psycho" was "a terrible thing." His uncle felt the same way, but expressed himself less strongly.

The patient also had difficulties with his girlfriend, who was a dietitian at a Boston Hospital. His stomach symptoms were associated with his dates with this girl. The question of marriage or any sexual intimacy was brought up during one of their dates; the patient felt ill the next day and could not go to work. His girlfriend took him to the Medical Clinic. She told the medical student in the Psychiatric Clinic that she was "fed up" with the patient and wanted to break off the relationship. The patient appeared relieved.

The patient lived in Chelsea with his paternal grandmother and his paternal uncle. His father lived in Worcester with his second wife.

Past history revealed that the patient's mother had died of tuberculosis when he was three months old. After his birth she went steadily downhill and never had any contact with him. His grandmother took over his care. There were no feeding problems. At about one year of age

he was forcibly toilet-trained by his grandfather who was described as "sadistic." The grandfather ran the household with an iron hand and the patient was very fearful of his anger. The patient remembered that at the age of five his grandfather took him to the Boston City Hospital. He sensed something terrible was going to happen to him and had a temper tantrum. "I was tied down on a chair, and my grandparents left me. I realized then that nobody loved me. While I was tied to the chair, my tonsils were removed. I remember feeling the hairy and strong hands of the doctor, the rush of blood in my mouth and the pain that followed. I still remember the operation with great fear." He said that since that time he had felt "different and unwanted."

His father was away constantly and saw little of the patient. The uncle and grandfather were very strict. His grandfather had a low opinion of public schools and spent three or four hours every day going over the patient's lessons. The patient remembered being frightened by this tutoring. When he was nine, his grandfather died. The patient felt relieved, and then anxious and guilty about his feelings. His father remarried when the patient was eleven, and from then on he saw even less of him. His grandmother thought he should spend all of his time studying. He had no friends during his childhood. After graduating from high school, he worked in a newspaper office. At the age of nineteen he met the hospital dietitian with whom he started going steady.

Previous personality: The patient always had very few hobbies and few friends. He was somewhat withdrawn and lonely, and enjoyed reading. Both at school and at his place of employment, he worked hard.

Mental status: The patient was a tall, thin, young man, obviously apprehensive and tremulous. His hands shook and he spoke quickly. He seemed depressed. He talked about his fears. He was unusually intelligent, well oriented and showed some insight into his difficulties.

DISCUSSION

DR. ERICH LINDEMANN: Was all this information gathered from the patient?

DR. SIFNEOS: It came from the notes of the medical student and of Dr. Carter, from the examination made in the Medical Clinic and from my interviews with the patient. The summary given contained the brief information required at our intake conference in order to decide what to do.

DR. MARIA LORENZ: Is there any evidence that during his life there was a good deal of anxiety or panic reactions, or is this a rather specific incident to which he reacted? In other words, does the patient appear to be a hysterical and continually anxious person, or was this episodic?

DR. SIFNEOS: My impression is that it was lifelong. He had acute panic related to medical symptoms. The symptoms and panic led to a loss of twenty pounds in three months. He had panic reactions in relation to his uncle and grandfather. The episode at the National Guard Camp intensified his anxiety.

DR. CARL BINGER: What were his assets besides his intelligence?

DR. SIFNEOS: He was able to relate well; his work record was good. In spite of his handicapped background, I thought that he functioned quite well.

DR. GERALD CAPLAN: What was his motivation in seeking medical treatment? His girlfriend brought him in; did he himself want to come?

DR. SIFNEOS: He had wanted help but his fear of doctors prevented his consulting one. The girl helped him make the contact. Also, he knew we were not "the kind of doctors who used needles." He was relieved by the referral to the Psychiatry Clinic.

DR. HERBERT BARRY: What was his religious affiliation?

DR. SIFNEOS: He was Catholic.

DR. ELIZABETH R. ZETZEL: What was the nature of this job? Had he wanted to go to college?

DR. SIFNEOS: His job was in a newspaper office. He knew something about this kind of work because a relative of his owned a newspaper. He did not have enough money to attend college.

DR. BARRY: What was the degree of intimacy with the girl?

DR. SIFNEOS: When the subject of petting arose, the patient experienced stomach symptoms. When the girl left him, he was relieved at not having to face sexuality any more. The girl, who was also being treated in our clinic, was understanding. She also had sexual phobias.

DR. CAPLAN: Did he say anything about the National Guard duty that would produce evidence about his relationship to men?

DR. SIFNEOS: Only that his symptoms started at the camp.

DR. ZETZEL: One should weigh the factors for and those against accepting the patient for treatment, taking into account the waiting list, the points in his history and behavior which would make one believe that he could be improved by psychotherapy, possible difficulties, and deciding whether a student or experienced therapist would handle him.

DR. LINDEMANN: At the Human Relations Service in Wellesley we would think chiefly about whether we could treat this patient, and what would happen to him if he were not treated. What factors in his life might lead to resolution of his problems? How much would this man have to master with or without treatment? In our Clinic, we are looking particularly for patients who will improve with treatment.

DR. ZETZEL: Untreated, this boy was likely to run into considerable difficulty. We had to weigh the relative weight of chronic and acute aspects. Did we believe that this was a recent anxiety state superimposed on something more chronic? Should we, in treatment, attempt to solve the acute aspects, or embark on a longer form of therapy with a view to resolving deep problems of a chronic status.

DR. LINDEMANN: Probably the group will agree that this patient is treatable and that we should refer him to a reasonably competent therapist. At an intake conference, would you also make a diagnostic formulation?

DR. SIFNEOS: Yes.

DR. LOVICK C. MILLER: Do you think psychologic tests would have been important at this point?

DR. SIFNEOS: Yes. A Rorschach test might at least have given us hints of what was to come.

DR. BINGER: It is difficult in the first interview to assess the importance of schizoid elements. A psychologic test might have helped.

DR. LINDEMANN: Psychologic tests might have indicated a different therapeutic approach.

DR. JOHN C. NEMIAH: I believe this is basically a hysterical problem. What we are seeing is a regression to a level where separation anxiety is paramount, producing what seems to be disturbed behavior. I would expect, however, an ultimately good outcome, although you will probably have to work through a good deal of infantile material and behavior with him.

DR. BARRY: There are indications that schizophrenia might ultimately develop in this patient. Although his immediate symptoms appear to be psychoneurotic, we all feel rather uneasy about him. It is interesting that his mother died when he was only three months old. In a previous study of 1,700 psychotic patients, it was noted that 7 per cent lost their mothers during early childhood. This figure is significantly greater than in the normal population. Death of the mother is less frequently a prelude to neurosis, at least in male patients.

I have seen patients who had complaints similar to this man. When confronted with a possible heterosexual relationship, anxiety, nausea and vomiting developed. Several were Catholics in whom the usual conflict over sex was intensified by religious conflicts.

The most significant persons in this case would seem to be the grandfather who had a punitive role during childhood and the father who is still distant and inaccessible.

DR. MORRIS CHAFETZ: This discussion differs from an intake conference because Dr. Sifneos has hinted at something more ominous here, and our judgment is altered by that fact. At an intake conference, most of us would agree with Dr. Nemiah.

DR. CAPLAN: There is more to this case than the point that was made in regard to deeper sources of trouble. Could this person build up relationships with parental figures in his life? His early infancy is hazy. He says he had no contact with his mother. He had a reasonable relationship with his grandmother until she let him down in relation to the tonsillectomy at the age of five, under pressure from the savage paternal figure, the grandfather. He tells us he did not have much to do with people but concentrated on his work, which he did reasonably well. He made some adaptation until he had an acute breakdown at an age when he would have to appear as a man.

The fact that he was able to make some adaptation is a sign of strength. There was an acute situation when he had grown up, but earlier there was a definite sign of personality disorder. I should conclude that he had a fairly severe personality disorder relatively well compensated until the load exceeded the threshold; then he had to crack. If you could deal with the acute crack-up, you might help him, provided you did not go too far into the basic problem. If you wanted to do that, you would have to think about psychoanalysis.

DR. ZETZEL: I would agree. I was disturbed

by the anxiety symptoms precipitated by a situation which had homosexual meaning. He also had similar anxiety symptoms in relation to heterosexual impulses. Was there confusion about sexual identity? One should guard against his getting into a basic homosexual transference situation with the therapist, and try to strengthen the heterosexual situation. He might be able to function with a certain degree of loneliness, not getting too close to men or to women. The therapist would be in a difficult situation, owing to the double nature of the symptoms and the feeling of being abandoned.

DR. LINDEMANN: What would be a situation in which he could function? A situation in which he suffers loneliness; but this might not be tenable. Also there seems to be a curious selection of information here; there are much data about his early life, but the recent past is veiled.

DR. BARRY: If this patient were being handled by any therapist who was not exceptionally capable, I believe the prognosis would be guarded. With skillful management, I venture to predict that he would do surprisingly well. I would anticipate, however, that the course of therapy would be exciting for both the patient and doctor.

TREATMENT AND FOLLOW-UP STUDIES

DR. SIFNEOS: I shall divide the course of therapy into four phases: I saw the patient weekly. In the first interview he was actively grieving over the departure of the medical student, but seemed to relate well to me. He seemed to be quite dependent. I decided to be as superficial and as reassuring as I could. He described phobias about doctors and dentists. He said he could stand the pain of taking a blood test but added, "I might give in, and when you give in, you never know what is going to happen." In the subway he would cringe if he saw a large, hairy hand holding onto the strap, and had to move to another section of the car. Week after week, however, he came to the clinic with a smiling face. He started describing his dreams. He had a recurrent dream in which he would hear a noise while walking down a street, would turn, and see a man coming at him with a knife. He would then have a fight, but at the last minute could stand no more, and would turn his back and be stabbed. In another dream he was a knight carrying a sword, jousting with an enemy. As they fell to the ground, he would be on top, winning. As he started to strike, the sword would melt. Both these dreams were terrifying to the patient.

After four months of treatment his medical symptoms had disappeared. He regained the weight he had lost. His girlfriend abandoned him but he did not miss her too much.

When I told him I was going to Europe for five weeks, he asked if I were going to Sweden and Germany and said, "My father opened a German port singlehandled during the war." He said his father was really a great man and showed some positive feelings toward him.

Phase two of the treatment began when I returned. The patient had lost 15 pounds and had telephoned three or four times wondering if he should see someone else. He was depressed, his stomach symptoms had returned, and he was not working. He said all his relatives were saying he was a coward. He thought all relatives—his grandmother, his uncle and his father—had sensed a cowardliness in him. He thought someone was "coming at him." He said, "I can defend myself." The next week his condition was worse. A fellow at work one night had told him he looked thin, and the patient viewed this as an "attack." He became interested in target practice, reasoning that strong people carry weapons and guns. He learned to shoot fairly well and believed he could cope with people. He said: "I know what this is all about. I am a homosexual. Isn't that what my father meant?" In another interview he looked sullen and sad, took a gun from his pocket and put it on my desk. He told me not to worry, "you are the only person who protects me." He asked me what I thought about the gun, and I said it was a pretty one. He said he had four guns, and this was a small one. He was depressed, and I was apprehensive after the interview. He had forced me to discuss things I did not want to go into. He stated he believed that men were going to attack him. He said, "They won't get me, I'll shoot my way out even if I have to die." He wanted to know if I thought he was really a homosexual. I discussed this disorder with him and pointed out that friendship, even his relationship to me, may be thought of as having homosexual elements, but one would not label this as homosexuality. I said there was no basis for people thinking he had had homosexual relationships, and I told him I did not think he was a homosexual. He said, "You do not really know, that at the National Guard Camp, a man came in drunk,

missed his bed and got in my bed." He became very sullen, his hands shook and he perspired profusely. He said he thought the man did it purposely. He was scared to call out for fear the other men would label this "homosexual behavior." He reassured me that nothing happened, and that eventually the man went to his own bed. Two weeks later the same man got into someone else's bed, was discovered, and shortly afterward was discharged from the National Guard. I told the patient that this episode did not alter my opinion of him. He appeared greatly relieved.

After this interview, from May to August, 1951, a transformation took place. The patient felt much better. He resumed work and decided that he wanted to get his girlfriend back, and knew how to go about it. In the last interview of this phase of the treatment he said he felt good enough, and announced to me triumphantly that he was engaged to his former girlfriend. He said, "I won her over and furthermore psychotherapy cured her sex phobias." He said she preferred him to every other man she had gone out with, and added, "Isn't this proof of my masculinity?"

Phase three began when the patient said that he had been drafted, and would have to have blood tests. He said he could not stand this, and would rather shoot himself. He appeared quite depressed. He said he had stopped working from worry about being drafted. I suggested that he should see the psychiatrist at the draft board and explain his phobia. "The psychiatrist might be able to make things easier for you," I added. In the next interview the patient was jubilant. The psychiatrist at the induction center did help him. He was deferred and no blood tests were taken. Following this he improved markedly. He decided to get married in December, and returned to work once more He had sexual relations with his girlfriend. His father met her, liked her, and said: "You are a good son of mine; you are growing to be a man after all." In November the patient was upset about having to have premarital blood tests. His fear of needles was just as great in spite of other improvements. He said he could not have a blood test unless I personally took the sample. A week before the marriage he still had not had the test. I wondered about taking it myself, because I thought it important that the marriage should take place as planned. I decided, however, against it because the patient seemed to be "acting out." Two days before the marriage he came in, looking sullen. He had had the blood test. He said, "I felt as if something had happened to me, my childhood protection is gone, yet I feel free."

Phase four consisted of follow-up study one month later when the patient returned. He had had a "wonderful wedding" and a "wonderful honeymoon." He said his wife was pregnant, and he expected to have a son. Regular interviews ended at this time.

I saw him again when his grandmother, to whom he was so attached, died in May, 1952. He had normal mourning for about two weeks. He knew it would have made her happy, he said, if she had known his child. Since his wife was Rh-negative, he had to have another blood test which was easily accomplished. In August he reported to me the birth of an 8 pound daughter. We discussed daughters and how wonderful they are. He was jubilant.

He was drafted and went to Korea for two years. He returned in excellent spirits. He now has a second child, a son, and lives happily with his wife.

DISCUSSION

DR. CARL BINGER: Did you ever discuss with the patient the legality of his carrying a gun? If a psychiatrist thought a patient might use a gun, what would his responsibility be toward society?

DR. SIFNEOS: I was apprehensive about the gun but I believed that he would not use it.

DR. LINDEMANN: On one side is the legal responsibility, and on the other the importance of having the patient know that he is trusted by the therapist.

DR. CAPLAN: A patient once told me he was going to poison his girlfriend because he thought she was being unfaithful to him. The next day he was put in prison for poisoning her. The first thing he told them was to call Dr. Caplan. Obviously this was to show me that he meant what he said.

DR. BINGER: In spite of the excellent outcome of this case, we should not necessarily draw diagnostic conclusions. A patient with psychoneurosis with this degree of disturbance might not recover so quickly. I am not at all sure that this was not a schizophrenic episode with paranoid features.

DR. ZETZEL:[9] This patient was presented to me in the clinic just before he was married. I was disturbed about him but believed there was a chance that he could come through as he did.

Ominous signs were noted. There was a suggestion of something psychotic with ideas of reference, of people commenting on him and following him. It was difficult to tell how much this patient dramatized. The fact that he responded so quickly to Dr. Sifneos' talk suggests an element of dramatization. It seemed as if he could be brought back to reality. This type of patient shows how dynamically close a hysterical condition can be to a schizoid condition. He could have gone one way or the other. I do not know what would have happened if his girlfriend had not returned to him. There were many chance features which enabled him to come back to something better than his previous adjustment.

Dr. Barry: I agree with Dr. Binger that this man was schizophrenic. This had been predicted on the basis of the partial presentation of his history. One might say that he was a compensated schizophrenic. I would have worried most about him when he was sure that people could read his thoughts and when he thought he was being followed. It took rare courage not to sign a commitment paper at that time. The question of the doctor's responsibility for a patient who carries concealed weapons is, as Dr. Binger states, a serious problem. If I had been called on to decide whether he should be hospitalized I would have made my decision on a day-to-day basis. I should have looked for evidence that he was acutely psychotic; in other words, I would have considered whether his schizophrenia was acute rather than latent. To be specific, if Dr. Sifneos had discovered evidence of hallucinations at the time he was carrying the gun he would have had no choice but to sign a temporary case paper. I assume Dr. Sifneos believed he had enough rapport with the patient to be sure of his ground. He knew him well enough to be certain that his ego strength was adequate to keep him from actually using the gun. The risk seems to have been justified by the outcome.

It is striking that the patient's defenses disintegrated when Dr. Sifneos went to Europe. Doctors' vacations are always a problem. The number of exacerbations when the psychiatrist goes away or when there is a change of service on the ward can be a very real problem.

Dr. Sifneos: In making my decision about what to do about the gun I found it helpful to think of our psychotherapeutic relationship. I was impressed by the patient's good relationship to me. His description of ideas of reference was not like the ones one hears from psychotic patients.

Dr. Maria Lorenz: The fact that this patient was carrying a gun was rather serious acting out. For a while he had been blocking in identification with masculinity. During the process of therapy he presented a prophetic dream showing what happened when he put himself into a masculine role. Apparently he carried this into a real life situation and became more aware of the opposite side. He tried to show that he was masculine, too. The turning point in therapy came in making the therapist the model for identification. The therapist did not appear violent and aggressive. He encouraged the patient's view of himself as a masculine person.

Dr. Lindemann: This is an interesting formulation, suggesting that the passivity was a counterpart of defense against a cruel form of masculinity. This is an example of long term contact with a patient, possible only in ambulatory patients. On the ward one cannot stop acting out. The clinic offers a wider horizon than the ward.

I believe the therapist is still important to this man and that he still admires him. Even though he has only two or three interviews a year this may figure in a good many decisions he has to make. If the therapist moved away the clinic might have to reach out for the patient. It is an interesting case.

Dr. Sifneos: After a few interviews with the patient it was my impression that his difficulties could be overcome with psychotherapy. I thought that he had not matured emotionally, that he was in a sense a preadolescent. It was like training an eight-year old boy, with the intellectual and physical development of twenty-one years, to deal with problems that he was not emotionally ready to cope with. I thought he needed me most as a person who would help him "grow up." My active support, "lectures," and reassurance were probably more those of a teacher and father than of a psychotherapist. After we established a good relationship he was willing to look more deeply into his problem and realize his strength rather than weakness. After he tested this strength by getting engaged and finally marrying his estranged girlfriend, his doubts about his masculinity disappeared, his physical symptoms and phobias vanished, and he was convinced about the fact, which I never doubted, that he was "a man."

SUMMARY AND CONCLUSION

A twenty-year old office clerk complaining of epigastric pain, nausea, vomiting, weight loss and feelings of insecurity and anxiety was referred by the Medical Clinic to the Psychiatric Clinic. The physical examination and the laboratory tests were negative. After an intensive psychiatric evaluation, he received intensive psychotherapy for one year and four months. At the end of that time he was symptom-free and emotionally well adjusted. The follow-up lasted about three years. His medical symptoms never returned.

The nature of the psychiatric treatment was essentially supportive. After a good relationship was established the patient was helped to "grow up." This was accomplished by helping him realize his strength. He became progressively more self confident and is at present leading a happy life with his family.

Clinico-pathologic Conference

Acute Gastroenteritis

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient (No. 205929), a sixty-nine year old unmarried woman, was admitted to Barnes Hospital for the first time in February, 1952, and died during her third admission on October 21, 1955.

The patient gave a history of having passed, intermittently, grossly bloody urine for four months prior to her first admission in February, 1952. Past history revealed an injury at four years of age resulting in a marked scoliosis and shortening of the right lower extremity. The patient had had mild dyspnea on exertion for some years prior to admission, and often complained of aches in the muscles of the upper extremities and shooting pains in the lower extremities. Physical examination revealed the deformity as described without other abnormalities. Cystoscopy demonstrated a chronic urethritis and two papillary tumors in the bladder. A complete blood count was essentially normal and urinalysis revealed a specific gravity of 1.020, 1+ proteinuria and a sediment packed with red blood cells and a few white blood cells. At the time of cystoscopy the papillary tumors were fulgurated and the pathologist's report of a biopsy specimen of one of the tumors was "transitional cell carcinoma, grade II."

The patient was readmitted in May, 1952, because of one episode of bleeding from the urinary tract and mild symptoms of dysuria. Once again cystoscopy was done and another papillary tumor seen. A biopsy specimen of this tumor was taken; the tumor was fulgurated. The pathologist's report was "transitional cell carcinoma, grade I."

The final hospitalization was in October, 1955, when the patient was admitted with the chief complaint of severe abdominal pain, nausea, vomiting and diarrhea of seven hours' duration. She was in a semi-stuporous state and the history was not entirely reliable. Apparently she had had no further urinary tract symptoms following the last fulguration. She stated that she had been quite well until seven hours prior to admission when she passed a diarrheal stool following which she had nausea and vomiting and the onset of severe abdominal pain. The pain was severe, cramping and unrelenting. Between the onset of her symptoms and her admission she had several bouts of vomiting and diarrhea. She did not note any blood or coffee-ground material in her vomitus nor did she have tarry stools or bright blood in her stools. She was seen at her home by a physician who found her writhing in pain and administered morphine and atropine. At the time of admission she complained bitterly of severe pain in her left foot. She denied ever having had similar symptoms prior to this attack. She stated that she occasionally took antacids for indigestion.

Physical examination revealed her blood pressure to be 40/20; pulse 128, respirations 20 and temperature 36.9°C. The patient was a well developed, deformed, elderly white woman in acute pain lying on her right side. She was obtunded, fairly cooperative and oriented as to time, place, and person. She was lethargic and dropped off to sleep easily only to be aroused frequently by pain in her abdomen and foot. The skin was dry, warm, coarse and of poor turgor. Lymphadenopathy was not detected. The marked deformity of her spine and shortening of the right leg were as previously described. There was no localized weakness or loss of joint mobility. Examination of the eyes, ears, nose and throat was not remarkable. The neck was supple. The heart was not thought to be enlarged. The rhythm was regular and no murmurs were heard. No lesions were noted in the breasts. The lungs were clear to percussion and auscultation. Examination of the abdomen revealed it to be

obese and slightly protuberant. There was a sense of resistance on the right side of the abdomen especially in the right upper quadrant where some rebound tenderness was noted. Bowel sounds were not heard. A fluid wave was not elicited. The liver was questionably palpable 3 cm. below the right costal margin. The spleen and kidneys were not felt. Pelvic examination revealed a virginal introitus and on examination with one finger no abnormalities were noted. Rectal examination revealed a tender mass in the right parametrium which could not be well defined. The neurologic examination was within normal limits.

Laboratory data on admission were as follows: packed red blood cell volume, 52 per cent; white blood cell count, 23,800 per cu. mm.; differential pattern: metamyelocytes 3 per cent, band forms 4 per cent, segmented forms 80 per cent, lymphocytes 7 per cent and monocytes 6 per cent. The red cells appeared normocytic and normochromic with 1+ poikilocytosis and 1+ anisocytosis. Urinalysis revealed a specific gravity of 1.020 with acid reaction, trace of protein and no sugar The microscopic examination revealed one hyalin cast, two to three red blood cells and one to two white blood cells per high power field. Stool: a finger specimen was guaiac-positive. Blood cardiolipin test gave a negative result. Blood chemical determinations: an amylase drawn upon arrival in the hospital was 400 units. The remaining determinations were obtained on the day following admission: amylase 200 units; non-protein nitrogen 47 mg. per cent; cholesterol 195 mg. per cent; calcium 10.8 mg. per cent; alkaline phosphatase 3.6 Bodansky units; sodium 137 mEq./L.; potassium 3.7 mEq./L.; chloride 96 mEq./L.; CO_2 15.9 mEq./L.; serum bilirubin, less than 0.8 mg. per cent; cephalin cholesterol flocculation, negative; thymol turbidity 0.3 unit; total serum protein 7.0 gm. of which 4.6 gm. was albumin and 2.4 gm. globulin. An electrocardiogram taken immediately on admission was interpreted as showing sinus tachycardia, but was otherwise normal. An electrocardiogram taken the following day showed an abnormal form of ventricular complex with periods of auriculoventricular dissociation and nodal premature contractions. Roentgenogram of the abdomen taken on admission was interpreted by the radiologist as showing a congenitally dislocated hip on the right, marked scoliosis of the lumbar and dorsal spines, question of pyloric obstruction manifested by a dilated air-filled stomach with hardly any air noted within the intestinal tract. A film of the chest revealed the spinal abnormality already described without other apparent abnormalities.

The patient was treated with Wangensteen suction and was given fluids containing l-norepinephrine intravenously. The blood pressure rose to 98–120/40–70. Material obtained from the stomach by Wangensteen suction was brown in color and strongly guaiac-positive. The packed red blood cell volume remained constant. During the first twelve hours in the hospital the patient excreted only 160 cc. of urine and 300 cc. of fluid per gastric tube. She received a total of 2,500 cc. of glucose in water during this time. At this point the hematocrit was 53 per cent. Fourteen hours after admission exploratory laparotomy was performed using local anesthesia. A small amount of serosanguineous fluid was noted in the peritoneal cavity. Nine inches from the ligament of Treitz a segment of jejunum about four inches long appeared thickened and edematous; when it was opened, an area of acute hemorrhagic ulceration was found with a coat of fibrin over the ulcer. This segment of bowel was resected. The blood supply to the entire bowel appeared normal. The stomach was opened and on the greater curvature at about its midpoint there was a 2 cm. hemorrhagic ulceration coated with fibrin. This was also removed. The liver appeared small and somewhat yellow. A biopsy specimen of the liver was taken. Fibroid tumors of the uterus were noted. The following comment was made by the surgical pathology department on the specimens submitted: "Sections of the liver biopsy are not remarkable except for the presence of scattered glycogen vacuolization of liver cell nuclei and lipochrome pigment in some liver cells. The portal areas show some interstitial hyalinization. Section of the stomach biopsy shows focal acute congestion, edema and leucocytic infiltration of the mucosa and submucosa with superficial erosion of mucosal lining. Sections of the jejunum reveal an acute congestion with hemorrhage and superficial necrosis of the mucosa and submucosa. Leukocytic infiltration of the mucosa and submucosa is present. The muscle coat is not involved by the inflammation except for some edema. No bacteria or fungi are noted." Following the operation, the patient's blood

pressure continued to fall in spite of the infusion of l-nor-epinephrine; she died twenty-one hours after admission.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: Dr. Harold Roberts, who saw the patient in her home, informed me that in addition to the marked abdominal pain she complained of severe pain in both arms. Apparently the pain disappeared by the time she was admitted to the hospital because the patient did not mention it, nor is there any record of arm pain in the hospital chart.

By way of summary, this sixty-nine year old practical nurse had a congenitally dislocated hip on the right which resulted in marked scoliosis. She was first admitted to Barnes Hospital in February, 1952, with the history of gross hematuria of four months' duration. Cystoscopy revealed a chronic urethritis and two papillary tumors in the bladder. One of the tumors was examined histologically and showed "transitional cell carcinoma, grade II." Both tumors were fulgurated. The patient was readmitted three months later in May, 1952, following a single episode of hematuria and dysuria. Repeat cystoscopy showed another papillary tumor which was biopsied and then fulgurated. This tumor was classified by the pathologists as "transitional cell carcinoma, grade I." Dr. Cordonnier, would you review the natural history and usual clinical course in this type of tumor? I would also like you to discuss the treatment of such tumors.

DR. JUSTIN J. CORDONNIER: The characteristic finding in papillary carcinoma grade I is, in general, the lack of muscle invasion. Unfortunately, in the pathologic report given in the protocol no mention is made of possible muscle involvement. The tendency of superficial tumors to recur is of the utmost importance. I would not be at all surprised if papillary carcinoma in the urinary bladder is found at postmortem examination. That is not to imply, however, that the tumor will be symptomatic. These tumors are quite readily amenable to transurethral resection and fulguration at the base, as was done here.

DR. REINHARD: We did not include the entire surgical pathology report in the abstract. Muscle involvement was not however specifically mentioned. The report was as follows: "The sections show grade II transitional cell carcinoma. The epithelium is very much thickened in most areas. Only a rare mitotic figure is seen. Slight pleomorphism of the cells is seen. The stalk contains relatively large masses of transitional cells."

DR. CORDONNIER: It should be noted that papillary carcinoma of the bladder not only has a marked tendency to recur, but also to develop new tumors in adjacent areas.

DR. REINHARD: Dr. Nicolai, would you discuss briefly the prognosis of this type of cancer and compare the five-year survival time following simple fulguration with that following cystectomy.

DR. CHARLES H. NICOLAI: The grading of such tumors depends upon two features. One classification, that of Jewett, depends upon the depth of penetration by the tumor into the bladder wall. This classification apparently has more prognostic value than does the classification of Brödel which depends upon the degree of anaplasia of the tumor. The chances for a five-year survival of a patient with a papillary carcinoma classified as grade I according to Brödel, or "superficial" according to Jewett, is 80 to 90 per cent. The recurrence rate, however, is 50 to 60 per cent within five years. The other extreme is a 0 to 5 per cent five-year survival for the most malignant tumors. We believe that fulguration is applicable only to the more superficial lesions and that total cystectomy is indicated for the more penetrating tumors. Total cystectomy has, in several authors' series, carried a five-year survival of 30 per cent. Comparing the results of fulguration and of cystectomy is more or less impossible, as each approach has its specific indications which in general do not overlap.

DR. REINHARD: Dr. Ackerman, is there any other malignancy of an internal viscus which can be treated by simple fulguration with a five-year survival rate approaching that which apparently can be obtained in this particular type of cancer?

DR. LAUREN V. ACKERMAN: I believe that fulguration will sometimes be successful in the treatment of bladder tumors. I cannot recall any other malignant tumor for which the treatment is fulguration. Some of the superficial skin cancers may be treated in this manner, although I would not recommend it, because all basal cell carcinomas grossly are not always basal cell carcinomas microscopically. If one makes a mistake and places a cautery in the middle of a "basal cell tumor" which in reality is a malig-

nant melanoma, that does not usually work out to the best interest of the patient.

DR. REINHARD: Perhaps it is fair to summarize by stating that one can expect a fairly good survival rate with simple fulguration. If there is recurrence, one can fulgurate the lesion again. Certainly total cystectomy is a very formidable procedure which in itself offers a real threat to the patient's further survival because of complicating ascending infections of the urinary tract. Would you care to add anything, Dr. Cordonnier?

DR. CORDONNIER: The most optimistic statistics analyzed show approximately a 45 per cent five-year survival for treatment with fulguration, which includes all grade I as well as grade II tumors. To say that the results are very good is, I believe, completely wrong. The results are not good, even in the most optimistic series. Obviously we do not like to perform cystectomies in cases of grade I and the early superficial grade II lesions, but I strongly believe, and I think Dr. Ackerman will bear me out, that we are still dealing with cancer and to rely on repeated fulguration in high grade malignancy is a mistake.

DR. REINHARD: What is the survival expectancy following cystectomy, Dr. Cordonnier?

DR. CORDONNIER: In our total series of approximately forty-four patients we have a 31.5 per cent survival rate. Included in that series are many tumors of high grade malignancy. Of these patients several had far advanced disease. Some were grade III and IV, and one patient had penetration of the entire bladder wall. It is a little difficult to compare figures for cystectomy with those for transurethral resection because urologists usually resect the easy cases and do cystectomies on the difficult ones.

DR. REINHARD: Dr. Ackerman, when these tumors do metastasize, where do they go?

DR. ACKERMAN: At one time Dr. Royce and I reviewed all the cancers of the bladder treated at the Barnes Hospital, and I can substantiate what Dr. Cordonnier has said. All those patients with microscopically undifferentiated tumors treated by fulguration died. Occasionally patients with benign looking tumors can be treated by fulguration, but many of these cases also get into trouble. It is very unfortunate that when cancer of the bladder metastasizes, it spreads to the muscle. The bladder has many lymphatics in the immediate area which the tumor quickly invades. Invasion to nodes along the aorta and through the vertebral vein plexus leads to distant metastases. Frequently, however, direct spread to contiguous structures, as well as regional lymph node involvement, is very important.

DR. REINHARD: We cannot exclude the possibility that the patient might have recurrent carcinoma of the bladder, although that is unlikely. We certainly cannot exclude the possibility of metastatic tumor, but I cannot see that this lesion could have been the cause of the patient's acute terminal illness. Would you agree?

DR. CORDONNIER: Yes.

DR. REINHARD: This patient was semistuporous on admission to the hospital, and the history was considered relatively unreliable. Apparently the patient had no urinary tract symptoms following the last fulguration. She stated that she had been quite well until seven hours prior to admission when she passed a diarrheal stool following which she had nausea and vomiting, the onset of severe abdominal pain and severe pain in the arm. The abdominal pain was severe, somewhat cramping and unrelenting. Between the onset of her symptoms and her admission to the hospital she had several bouts of vomiting and diarrhea but did not note any blood in her stools or tarry stools. Prior to admission she also complained bitterly of severe pain in her left foot. She denied ever having similar symptoms prior to the immediate attack. On admission she was in shock. The blood pressure was 40/20 and the pulse, 128. Temperature was normal. Only two temperature determinations were done at the hospital; one on admission and one the following day which was 38.2°C. The patient was obtunded, lethargic and dropped off to sleep very easily, perhaps as a result of the morphine administered before admission. She was aroused frequently by severe pain in the abdomen and in her foot. The abdomen was obese and protuberant. There was a sense of resistance on the right side of the abdomen, particularly in the right upper quadrant. There was some rebound tenderness in this area. The liver edge was questionably palpable. Dr. Powers, would you review the roentgenograms?

DR. WILLIAM POWERS: This patient had marked scoliosis of her dorsal spine. Her stomach was noted to be markedly dilated and there was no free air beneath the diaphragm. There was a large amount of radiopaque material within her pelvis, probably metallic in nature,

which the patient had presumably ingested. A dislocated left hip was also seen.

DR. REINHARD: Dr. Powers informs me that the radiologists believed the metallic material in the pelvis was probably bismuth. However, there is no mention in the chart that she had received any bismuth orally.

DR. W. STANLEY HARTROFT: It could be the antacids which she took frequently.

DR. REINHARD: It could possibly have been some antacid containing bismuth. Subsequently laparotomy was performed and the patient was found to have an area of inflammation and ulceration on the greater curvature of the stomach and a similar ulceration of the jejunum. In view of these findings I believe we should consider the possibility of suicide or poisoning. Dr. Bergner, this woman was your patient. She was an unmarried, crippled, elderly person. What kind of a woman was she? Had she ever had symptoms suggesting depression or neuropsychiatric symptoms of any sort?

DR. GRACE BERGNER: She was an amazingly stable person. She worked hard every day as a practical nurse and in spite of her marked spinal deformity did a splendid job. The case that she was on was that of a cantankerous old man who swore a lot. She became a little depressed and upset when he would swear at her but ordinarily she took things in her stride. I did not have an opportunity to see her, however, during the month prior to her final admission.

DR. REINHARD: Dr. Robins, does this information exclude the possibility of suicide, or does an occasional person who is apparently perfectly well from a neuropsychiatric standpoint suddenly get tired of life and commit suicide?

DR. ELI ROBINS: There are few data on successful suicide which are of much value to the physician in dealing with an individual patient. There are data on patients who have made apparently serious (genuine) suicide attempts but who survived them and could be interviewed. A recent study by Batchelor and Napier in the United Kingdom and a study which we did in St. Louis show quite comparable data concerning serious suicide attempts in patients over sixty years. There was a total of fifty-nine patients over sixty years of age in the two studies. Based on these data, the answer to your question as to whether a patient perfectly well from a psychiatric standpoint will commit suicide is no, with the possible exception of patients with a chronically painful and/or disabling medical or surgical illness. The diagnosable illnesses that may lead to suicide in this older age group are: (1) chronic brain syndrome (dementia); (2) acute brain syndrome (toxic psychosis); (3) chronic alcoholism and (4) manic-depressive psychosis, depressed phase. From the hospital data and Dr. Bergner's information the first three of these may be excluded. A number of apparently stable persons may have their first episode of this illness after the age of sixty. Although this patient was psychiatrically well a month before her death, according to the information from Dr. Bergner, a psychotic depression may have developed during that interval.

DR. REINHARD: The depression might have come on very suddenly.

DR. ROBINS: It may come on in a week or two.

DR. REINHARD: Dr. Recant, if this patient did die of poison, what poisons do you think we would have to suspect?

DR. LILLIAN RECANT: The most likely agents are the metallic poisons of the arsenical and mercury group. The chief reason for suggesting these are their ready availability in various compounds that are on the market such as the arsenicals in rat poisoning substances and mercury in mercuric chloride. If one considers the symptoms presented in this case, the most probable agent would appear to be arsenic, and arsenic trioxide is the most commonly used of the arsenicals in either suicide or homicide attempts. This material is a soluble white heavy powder which has only a very faint taste, and so can be used in various liquids without being easily recognized. It produces three categories of poisoning. The first kind is called the acute paralytic type, which is usually induced by a fairly large dose and is a rapidly fatal syndrome. Following a large dose, the major symptoms are those of circulatory collapse and coma; death usually occurs within twenty-four hours. The second and most common type of poisoning is the gastrointestinal variety, characterized chiefly by vomiting immediately after the drug is ingested. This patient described diarrhea and then vomiting following the diarrhea. The sequence is somewhat unusual, although the history may be unreliable. Vomiting occurs after the drug is taken, and one or two hours later diarrhea ensues. Accompanying these symptoms there may be very severe abdominal pain and protracted vomiting and diarrhea with blood staining of the vomitus and stool. At the same time, cramps have been noted in the calves of

the legs and in the musculature. The mechanism of these is not clearly known. The basic findings at autopsy in patients with this sort of semiacute gastrointestinal involvement include lesions in the stomach and the intestine as well as lesions of the myocardium. The gastrointestinal involvement appears as superficial ulceration. Rarely a jejunal ulcer, as well as a stomach ulcer, may be noted with no lesions in the duodenum.

DR. REINHARD: Would you expect a diffuse inflammation and ulceration of the stomach and the jejunum rather than a localized ulcer?

DR. RECANT: Yes, I would, but apparently localized ulcers can occur. Fairly specific lesions in the endocardial areas described as flame-shaped hemorrhages may occur which can produce very striking changes in the circulatory system. It should be noted that this patient did have electrocardiographic changes on the second day, although there are probably many other reasons why these changes could have occurred. Finally, the liver may be involved. In acute cases, one does not expect to see very much in the liver except hydropic degeneration and some evidences, perhaps, of minor fat infiltration and inflammation. Of course, in the subacute and more chronic cases, subacute yellow atrophy with jaundice and a variety of other findings occur.

DR. REINHARD: Do you think this patient died of metallic poisoning?

DR. RECANT: Yes, I do.

DR. REINHARD: Dr. Powers, would either mercury or arsenic cast a roentgenographic shadow like that seen in this patient's films.

DR. POWERS: These metals do cast shadows as evidenced by the fact that they are seen in the buttocks of people who have received antisyphilitic therapy.

DR. REINHARD: This is usually bismuth, however.

DR. POWERS: Arsenic has been used, and arsenic will be visible within the intestine.

DR. REINHARD: Dr. Rosenbaum, could this patient have had a Cushing ulcer? That is, a gastric ulcer seen in association with tumors or other lesions in the vicinity of the hypophysis?

DR. HERBERT ROSENBAUM: It is possible to develop gastric ulceration with lesions of the hypophysis. Dr. Cushing's series was based on people with frontal lobe tumors. However, in a recent paper, French and his colleagues carried out an experimental study with monkeys and showed that it was possible to produce gastrointestinal lesions in six of a total of seventeen monkeys by stimulation with chronically implanted electrodes in the region of the hypothalamus. These ulcerations were of two types; either a localized pre- or postpyloric ulceration or, in two instances, a rather diffuse ulcerative process throughout the upper gastrointestinal tract.

DR. REINHARD: I believe we should now review the pathologic material obtained from the stomach and the jejunum at laparotomy.

DR. HARLAN J. SPJUT: The sections of the stomach showed a superficial erosion involving the upper mucosa with extravasation of blood in that area. There were no changes whatsoever in the submucosa or in the muscularis in the stomach biopsy specimen. The jejunum manifested several different changes. First, the villi appeared to be slightly thickened, due to some fibrosis plus the presence of a moderate number of capillaries, suggesting perhaps that there had been a chronic process going on in the jejunal portion of the bowel. Second, some areas showed very acute necrosis of the mucosa with extravasation of blood into the submucosa plus edema, and an acute vasculitis. The liver biopsy was interpreted as being essentially normal.

DR. REINHARD: Dr. O'Neal, you performed the laparotomy in this patient. Would you describe the extent of the lesion, its appearance and the appearance of the gastric and jejunal mucosa in areas distant from the areas of ulceration.

DR. LAWRENCE O'NEAL: First, I would like to comment on the patient's condition at the time of operation. She was in shock and somewhat stuporous, and nor-epinephrine was being given. The entire operation was done with approximately 50 cc. of 1 per cent procaine injected into the anterior abdominal wall as the only anesthesia. When the abdomen was entered, there was a very small amount of serosanguineous fluid. One of our preoperative impressions was mesenteric thrombosis, but the bowel was viable and the mesenteric arteries pulsated normally. Except for the stomach and small intestine, the only lesion encountered on exploration was a fibroid tumor of the uterus. The stomach was normal to inspection and palpation. It was opened only because fluid had been aspirated previously which contained blood. We found the superficial ulceration on the greater curvature. The jejunum was somewhat edematous through perhaps three feet. The serosa was normal. In a few areas there was a

bluish cast to the intestine. When the jejunum was opened at what appeared to be the most involved area, several superficial ulcers and edema of the mucosa were seen. This segment was excised for biopsy purposes. More of the jejunum was involved, but this one area was the worst.

DR. REINHARD: There was, therefore, involvement of a fairly wide area of the jejunum with as many as a dozen ulcers in all.

DR. O'NEAL: I believe most of those were in the one segment, and the rest of the involvement was somewhat minimal. There was some edema and occasionally a blue cast to the rest of the intestine.

DR. REINHARD: Dr. Harford, do you know of any acute bacterial infection of the upper gastrointestinal tract that would be apt to produce these findings? Would you discuss the possible etiology if this is a bacterial infection.

DR. CARL G. HARFORD: One thing which might be considered is food poisoning due to staphylococcal enterotoxin. Dr. Sherry has pointed out to me that there is a disease which involves the jejunum with a severe necrotic enteritis, due to a rare type of clostridum, type F. This clostridium is distinct from others in that it resists boiling for long periods of time. It also has more betatoxin and less alphatoxin than other types of clostridia. In the original report of this disease diffuse involvement of the bowel was present in addition to the involvement of the jejunum. From the point of view of infectious agents, it would seem to me that these would be the two most likely possibilities. There are many other infectious agents that can involve the intestinal tract, but I believe they are less likely. Shigella usually involves the colon. Salmonella could involve either the colon or the ileum, but characteristically causes a more prolonged illness and usually produces fever. There is no information about the pathologic picture in any type of viral enteritis, although I believe it has been established that there is such a thing. There are also many other organisms which can produce bacterial enteritis. Escherichia coli has been implicated as a cause of infantile diarrhea. Organisms such as pseudomonas, paracolon, proteus and even Streptococcus faecalis are believed to be capable of causing acute bacterial infections of the intestinal tract, but the evidence in these cases is not as distinct.

DR. REINHARD: Dr. Scheff, according to Bockus, acute bacillary dysentery due to dysentery organisms can produce an acute disease with death occurring within twenty-four hours. The temperature is usually elevated to about 104°F. but in some of the more acutely ill patients, Dr. Bockus mentions that prostration may be so great that the temperature may be subnormal. The white blood cell count may be low although it is usually elevated and may be as high as 50 or 60,000 cells per cu. mm. This patient had a very high white count. She did have diarrhea and abdominal pain, which was somewhat cramping in character. Would you tell us whether ulceration of the jejunum and stomach occur in bacillary dysentery?

DR. HAROLD G. SCHEFF: No, ulceration is usually not seen in bacillary dysentery. In bacillary dysentery, profuse diarrhea will often develop, with considerable tenesmus, blood, mucus and pus in the stool. This patient did not present that picture.

DR. REINHARD: The bowel was not opened. Is it possible that there was an inflammation of the bowel not apparent on its external surface?

DR. SCHEFF: I believe that if the patient had an acute bacillary dysentery, Dr. O'Neal would have noted it because the serosa would show evidence of inflammation.

DR. REINHARD: Would you tell us what acute phlegmonous gastritis or gastrojejunitis is, and should we consider this diagnosis?

DR. SCHEFF: Acute phlegmenous gastritis is always of bacterial origin, and is extremely rare. Usually there is involvement of the entire stomach with multiple abscesses. I would not consider that diagnosis here.

DR. REINHARD: Dr. Kenamore would you discuss the diagnostic possibilities in this patient?

DR. BRUCE KENAMORE: This case would fit the entity known as acute necrotizing jejunitis, which has a fairly characteristic roentgenographic picture. The clinical story is in keeping with that disorder. Three possibilities must be considered in the patient's diagnosis, one of which has been fairly well eliminated. At one time I believed she might have had unrecognized Addison's disease and that viral enteritis might have developed which was enough to throw her into the crisis of adrenal insufficiency. Secondly, she might have had acute necrotizing jejunitis, and finally she might have had metallic poisoning. I would consider necrotizing jejunitis as my first diagnosis because metallic poisoning should have provoked more renal changes and urinary tract findings than are reported here.

DR. REINHARD: Would you like to describe acute necrotizing jejunitis?

DR. KENAMORE: Necrotizing jejunitis is a disease described chiefly in the German and French literature. I could find but few clinical references in English. The etiology is unknown; some authors attribute it to a clostridium, but the specific agent has not yet been identified. It is characterized by inflammation of the mucosa with superficial abscesses, erosion and ulceration, usually confined to the jejunum but sometimes extending into the duodenum and into the ileum. It has a rather consistent radiographic picture. Clinically it is characterized by nausea, vomiting, diarrhea and very severe generalized abdominal pain. Patients frequently are operated upon, as this one was, more or less for exploration, without a definite diagnosis. Often they do not survive such laparotomy.

DR. RECANT: I would like to suggest that since acute necrotizing jejunitis is called a disease of unknown etiology, perhaps such cases are related to poisoning. Were any of them investigated with poisoning in mind?

DR. KENAMORE: Not to my knowledge.

DR. REINHARD: My final diagnosis is acute necrotizing jejunitis. I am not clear whether necrotizing jejunitis is a specific entity or whether it represents a clinical and pathologic syndrome that may develop as a result of any of several etiologic agents, such as poisoning, the effects of bacterial toxins, or, perhaps, the direct bacterial invasion of the intestinal tract.

PATHOLOGIC DISCUSSION

DR. DANIEL L. ROSENSTEIN: Examination of the body of this slightly obese white woman confirmed the presence of a marked dislocation of the right hip and severe scoliosis. There was a small amount of serous fluid in each of the body cavities, blood-tinged in the peritoneal cavity. The surgical incisions in the abdominal wall, stomach and jejunum were well closed. The right lung was reduced in size because of the thoracic deformity, and there were dense fibrous pleural adhesions over its posterior surface. The wall of the right ventricle of the heart was 5 mm. thick.

The intestinal tract below the esophagus was empty except for small amounts of yellow mucoid material which in the stomach was flecked with altered blood. The mucosae of the gastric fundus, jejunum and rectum were covered in irregular patches by a thin yellow-gray membrane. The mucosa was friable, granular, red and swollen. In the jejunum there were two sharply localized lesions that involved the entire circumference of the bowel, and here necrosis of the mucosa appeared more advanced. (Fig. 1.)

There was a moderate degree of central congestion of the liver. The remainder of the gross examination disclosed nothing of significance. In aerobic and anaerobic cultures of the intestinal contents, only E. coli grew.

Dr. Lauren Ackerman had suggested, when he examined the surgical specimen, that the lesions in this case were likely due to poisoning by a heavy metal. Therefore, a portion of liver that had been refrigerated since the time of autopsy was submitted to the Municipal Health Laboratory of St. Louis for a determination of its arsenic content. The liver contained 0.97 mg. per cent of arsenic. Fixed tissues, submitted for determination of arsenic content later, had probably been leeched of some of the metal, but the results of these analyses are of interest. The reported values, in milligrams per 100 gm. of tissues, are as follows: liver 0.283, ileum 2.760, jejunum 0.386, stomach 0.153, kidney 0.134, and pancreas 0.016. An arsenical concentration of over 0.04 mg. per cent of arsenic in a body at autopsy is abnormal.[1]

Death due to arsenical poisoning is not common; in thirty-one years the New York Medical Examiner's Office classified only 272 deaths as arsenical poisoning, and only thirteen of these as homicides.[2] I have found only two other cases of arsenical poisoning in our files.

DR. ROBERT M. O'NEAL: Microscopically, there were a few focal areas of interstitial myocardial hemorrhage and a slight degree of central necrosis of liver cells, no more than we usually see at autopsy in a patient who has been in shock for several hours. The other organs, except the intestine, were normal microscopically. The mucosa of the stomach contained essentially the same lesions that were present in the surgical specimen; marked congestion with extravasation of blood into the mucosa and an overlying membrane composed of necrotic epithelium, mucous, scanty fibrin, and a few erythrocytes. The rectal mucosa was severely congested and

[1] COPEMAN, P. and BODENSTEIN, J. An investigation of causes of arsenical poisoning. *J. Forensic Med.*, 2: 196, 1955.

[2] GONZALES, A., VANCE, M., HELPERN, M. and UMBERGER, C. J. Legal Medicine, Pathology and Toxicology. New York, 1954. Appleton-Century-Crofts, Inc.

FIG. 1. Gross photograph of one of the focal lesions of the jejunum. A glistening membrane covers the hemorrhagic mucosa. The bowel wall is thickened.

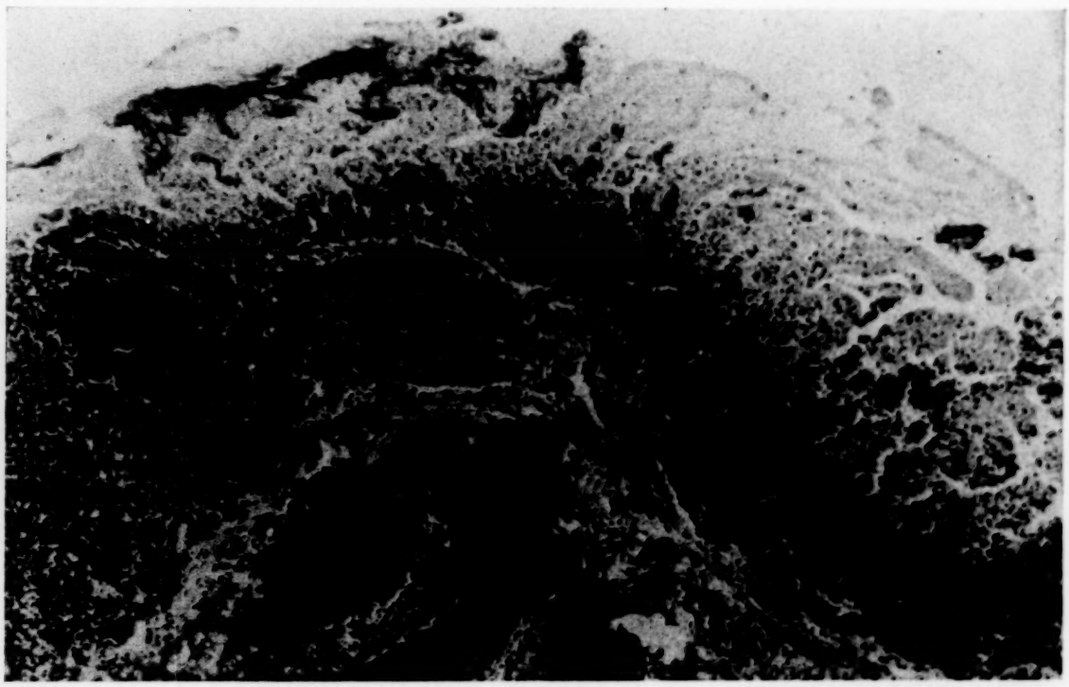

FIG. 2. Low power photomicrograph of the jejunal mucosa at one of the focal lesions. An incomplete membrane overlies the necrotic mucosa. The deeper portion of mucosa is markedly congested. The darkly stained mass of material surrounding the vessel in the submucosa is extravasated fibrin. Weigert's fibrin stain × 42.

its epithelial cells necrotic. Here the membrane was better defined and contained more fibrin and leukocytes, with an early polymorphonuclear leukocytic infiltrate in the submucosa. The focal lesions of the small intestine were sharply demarcated and its superficial mucosa was necrotic and severely congested. Fibrin exudate in the submucosa of these areas could be demonstrated especially well in microsections stained by Weigert's method. (Fig. 2.) Many venules in the submucosa had lost their endothelial linings. Their walls contained numerous polymorphonuclear leukocytes and nuclear debris. These damaged vessels may therefore have been the source of fibrin exudate in the submucosa illustrated in Figure 2. Arterioles were not affected. This type of reaction of vessel walls is highly characteristic of arsenical poisoning; the metal seems to exert a severe and selective effect on vascular endothelium, particularly in the intestine.

The lesions of the bowel are consistent with classic descriptions of arsenical poisoning. Intestinal lesions can occur even in cases in which arsenicals have been administered per vaginum to induce abortion. Arsenic is excreted by the kidneys and intestines, and apparently this fact determines the localization of lesions. The toxicity of arsenic is not usually due to its corrosive action, as it precipitates proteins only if present in very high concentration. The primary toxicity may be due to the affinity of arsenic for sulfhydryl groups in the cellular enzymatic system, leading thereby to cell death.[3] We do not know the amount of poison that this patient consumed, but the toxicity of an arsenical is related to its solubility, and as little as 0.1 gm. can cause death if administered under suitable conditions.

Final anatomic diagnoses: Primary: necrotizing lesions of the mucosa of the stomach, jejunum and rectum, compatible with acute arsenic intoxication; sutured, unhealed, right rectus surgical incision; sutured incision in the pyloric antrum of the stomach; sutured jejunojejunostomy, and sutured liver biopsy site; (history of exploratory laparotomy with biopsy of liver, stomach and jejunum, and of death in the recovery room); central necrosis of the liver, slight (history of prolonged shock); focal atelectasis of the lungs, moderate. Accessory: arteriosclerosis of the cerebral arteries, moderate, and of the aorta and coronary arteries, slight; congenital dislocation of the right hip; scoliosis to the right, advanced; fibrous pleural adhesions over the posterior portions of the middle and lower lobes of the right lung; cystitis cystica of the urinary bladder; scar on the left side of the posterior wall of the urinary bladder (history of removal of papilloma of urinary bladder).

Acknowledgment: Illustrations were made by the Department of Pathology, Washington University School of Medicine.

[3] Peters, R. Significance of biochemical lesions in pyruvate oxidase system. *Brit. M. Bull.*, 9: 116, 1953.

Case Reports

Constitutional Non-hemolytic Jaundice with "Lipochrome" Hepatosis (Dubin-Sprinz Disease)*

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FROM time to time jaundice of a chronic type is encountered in healthy young adults who show no evidence of abnormal hemolysis, biliary obstruction or hepatocellular disease. The recognition of this form of jaundice as a clinical entity dates back to the turn of the century when Gilbert and his associates[1,2] described a group of cases of acholuric jaundice without associated hepatic or splenic enlargement, under the heading of "cholémie simple familiale." Gilbert's name still remains identified with non-hemolytic, non-obstructive, acholuric jaundice of constitutional type, even though examples of mild hemolytic icterus, hepatic disease and carotinemia were probably included with his original cases.[3]

A number of thorough investigations of the nature of Gilbert's disease have appeared in the literature. In 1941 Dameshek and Singer,[4] reporting on two families, established the laboratory profile of the disease and also contributed the popularly employed designation "familial non-hemolytic jaundice" to the entity. In 1944 Comfort and Hoyne,[5] in a review of thirty-five cases collected from the records of the Mayo Clinic over a period of eight years, described the same condition as "constitutional hepatic dysfunction." Notable contributions have also been made by Meulengracht[6] who termed the disorder "icterus intermittens juvenilis" and by Alwall[7,8] who coined the name "hereditary non-hemolytic bilirubinemia."

Gilbert's disease is characterized by chronic or intermittent jaundice which begins during youth or early adult life and lasts for many years. The jaundice is seldom intense but it often becomes deeper after intercurrent illness, exertion or fatigue. Some diminution of jaundice is described with advancing years.[6] The patient remains in good health but in addition to jaundice frequently complains of lassitude, fatigue, dyspepsia and symptoms of functional type.[3,6,9] Several members of a family may be affected.[4,8,10] Usually the only physical finding is scleral icterus. Liver and spleen are not enlarged.[3] Serum bilirubin levels are usually under 5 mg. per cent, although maximal values of 10 to 12 mg. per cent have been recorded.[5,7] The van den Bergh reaction is of indirect type.[4,5,7] The urine is free of bile. There are no abnormalities of the blood, and the sedimentation rate is normal. The disorder may be differentiated from familial hemolytic jaundice by the absence of anemia, spherocytosis, reticulocytosis, abnormal red cell fragility, bone marrow hyperplasia and urobilinogen in the feces.[4] Normal values are obtained for liver function tests such as bromsulphthalein excretion,[4,5,11] thymol turbidity[9] and the Takata reaction.[7,9] The bilirubin excretion test is of significance in that the elimination of injected bilirubin from the serum is delayed.[4,10] Gallbladder function is usually normal as judged by cholecystography.[5,7] Liver biopsy specimens have repeatedly revealed only essentially normal structure.[6,7,9–11] Three autopsied cases are on record, but these have not contributed significantly to a better understanding of the disease.[10,12] On a basis of

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long-term follow-up studies prognosis is generally said to be excellent.[3,6] However, death from kernicterus may occur if the disorder becomes manifest during infancy.[10] The etiology of Gilbert's disease remains obscure. It is probably best regarded as an inborn error of hepatic function producing a high excretory threshold for bilirubin.[4]

In 1954 Dubin and Johnson,[13,14] and Sprinz and Nelson[15] outlined the features of a new, distinct clinicopathologic entity under the respective headings of "chronic idiopathic jaundice with unidentified pigment in liver cells" and "persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells." While this newly described disorder closely resembles Gilbert's disease with regard to symptomatology, age of onset and clinical course, it differs from the latter in the following respects:[14] (1) the presence of dark urine; (2) a higher incidence of bilirubinuria; (3) the serum bilirubin always gives an elevated direct van den Bergh reaction; (4) liver function tests such as bromsulphthalein excretion, cephalin flocculation and thymol turbidity often give abnormal results; (5) the gallbladder cannot be seen on cholecystography; (6) the liver exhibits normal structure but is grossly and histologically discolored by the presence of a coarse, brown pigment in parenchymal cells. Diagnosis in this disease can be established by a study of needle biopsy specimens, because of the pathognomonic histologic appearance of the liver.[14,15] On the same basis, conditions such as chronic viral hepatitis and obstructive jaundice, which may enter into the differential diagnosis of clinical grounds, can be excluded.

The two papers[14,15] which established the "Dubin-Sprinz disease" as an entity reported a total of sixteen cases, three of which were common to both series, judging from the protocols. These cases were derived from over 4,000 histopathologic reports of liver biopsy specimens on file at the Registry of Hepatic Pathology, Armed Forces Institute of Pathology. More recently Klajman and Efrati[16] described the typical findings of the disease in a young woman of German origin. Ours is the detailed report of an additional case with further investigative findings.

CASE REPORT

Sgt. M. S. P., a twenty-three year old white man, had been in good health until April, 1950, when "flu" developed. Symptoms included weakness, generalized aches and pains, nausea, diarrhea, dark urine and several grey-colored stools. Four weeks later (May 29th) the patient was admitted to Whitehorse Military Hospital with malaise, vomiting, anorexia, constipation and anergy. His urine was dark but stools were of normal color.

The patient had been born in Poland. Chickenpox was the patient's only childhood illness. There was no history of transfusions or exposure to hepatotoxins except that he had been drinking a bottle of whiskey per night "for some time." His father, aged forty-seven, was living and well. His mother had died in childbirth. Three siblings were in good health. There was no family history of jaundice or anemia.

On physical examination the only important findings were mild scleral icterus and moderate right upper abdominal tenderness. Bile and urobilinogen were present in the urine. The serum bilirubin was persistently elevated; it ranged from a level of direct 4.3/indirect 4.2 mg. per cent on admission to one of direct 2.2/indirect 2.4 mg. per cent on discharge from hospital, June 15, 1950. Because of these findings "infectious hepatitis" was suspected.

On October 3, 1951, the patient was seen at the outpatient department of the Colonel Belcher Hospital, complaining of blackouts and recurrence of previous symptoms. There was liver tenderness and enlargement to 3 cm. below the costal margin. Release from military service was proffered because of "chronic hepatitis" but the patient chose to remain in the Army.

He entered the University of Alberta Hospital on January 28, 1953, because of weakness, apathy and right upper abdominal discomfort, the latter being occasioned by sudden movement. Scleral icterus and right subcostal tenderness were the only significant physical findings. The urine contained bile and urobilinogen, the latter in trace to 3 plus quantities. The initial serum bilirubin value was direct 2.6/indirect 2.0 mg. per cent. Other laboratory data were as follows: cephalin-cholesterol flocculation, negative; bromsulphthalein retention, 8.2 per cent; total serum protein, 7.6 gm. per cent with 4.9 gm. of albumin and 2.7 gm. of globulin; alkaline phosphatase, 4.7 Shinowara-Jones-Reinhart units; prothrombin time, 74 per cent of normal. The gallbladder was not seen on cholecystography. The patient remained in the hospital for one month on a diet high in proteins and vitamins, supplemented with methionine. There was rapid symptomatic improvement and the van den Bergh reaction fell to direct 1.9/indirect 0.9 mg. per cent. His medical category was lowered in accordance with a diagnosis of "cirrhosis of the liver."

Although clinically well, the patient was seen on two subsequent occasions as an outpatient. Physical findings and laboratory results remained unchanged.

During December, 1954, he suffered a severe recurrence of previous symptoms, including nausea,

vomiting, weakness and dizziness. He admitted heavy drinking for the previous two months, against advice. In this regard he also complained of unduly severe "hangovers." He was confined to a local municipal hospital for two weeks and was then transferred to the University Hospital on January 6, 1955. Except for scleral icterus, physical examination was essentially normal. Laboratory data were as follows: hemoglobin, 16.1 gm. per cent; red blood cells, 5,140,000; white blood cells, 11,650; differential: segmented neutrophils, 43 per cent; eosinophils, 5 per cent; lymphocytes, 49 per cent; monocytes, 3 per cent; reticulocytes, 0.9 per cent; blood group, O Rh-positive; erythrocyte sedimentation rate, 2 mm. in the first hour (Westergren); Coombs' test, negative; erythrocyte osmotic fragility, normal. The serum bilirubin measured 4.8 mg. per cent (direct 3.0 mg. per cent, indirect 1.8 mg. per cent). Excretion of urinary urobilinogen ranged from 2.3 to 8.7 mg. in twenty-four hours. Complete urinalysis was normal. A test for porphobilinogen gave negative results. The Kahn reaction was negative. Normal values were also obtained for serum proteins, alkaline phosphatase, prothrombin time, heterophil agglutinins, thymol turbidity, cephalin-cholesterol flocculation and bromsulphthalein retention. The gallbladder was not seen on cholecystography but with a double dose of dye (telepaque®) there was some opacification of the organ; contraction occurred after a fatty meal. No calculi were noted. The patient was seen in surgical consultation and exploratory laparotomy was advised. This was effected on January 14, 1955, at which time the liver was found to be enlarged to several fingers below the right costal margin. It was described as "soft and dark in color." Exploration of the biliary tree failed to disclose any significant abnormalities. There was no splenomegaly. A liver biopsy specimen showed a striking centrolobular accumulation of coarse, dark brown pigment within parenchymal cells. On a basis of clinical and pathologic findings a diagnosis of "persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells" (as described by Dubin and Sprinz) was made. The patient was discharged from hospital, clinically well, two weeks later. His army category remained at its lowered status. It was recommended that he be rechecked every six months or sooner if necessary. To date he has remained well.

HISTOLOGY

The liver as observed at laparotomy was enlarged to several fingers below the right costal margin. It had a thin, smooth, shiny capsule. The underlying parenchyma was greenish black in color and of soft consistency. Incisional biopsy revealed mottled pigmentation which conformed to lobular structure. (Fig. 1.) Fixation of the specimen in 10 per cent buffered formalin produced only slight alteration in color.

Microscopically, the liver showed a normal lobular pattern. (Fig. 3.) There was no evidence of parenchymal damage, necrosis, regeneration, inflammation, fibrosis or congestion. (Fig. 4.) No bile thrombi were found. Liver cells were of normal size and displayed well defined cell membranes which enclosed finely vacuolated, slightly acidophilic cytoplasm. There was no alteration in reticulum framework. (Fig. 2.) The outstanding histologic feature was the presence of an amorphous, coarsely granular, brown pigment within the cytoplasm of liver cells. (Figs. 4 and 5.) This was observed to good advantage in cleared, unstained paraffin sections. The pigment tended toward an axial distribution so that a clear margin of cytoplasm was often found along the sinusoidal border of cells. (Fig. 4.) Pigment granules were of irregular outline but many approached an oval or spherical form. Their average diameter was 1.7 microns, with a range of from 0.5 to 4 microns. In some cells the pigment occupied up to half of the cytoplasmic volume. The most dense deposits occurred in pericentrally placed liver cells, with progressively smaller amounts in more peripherally located cells. (Fig. 3.) Even in portal areas, however, it was rare to find a liver cell which did not contain at least a few dust-like pigment particles. Uniformity in quantity and centrolobular distribution was maintained from one hepatic lobule to another. In accordance with criteria laid down by Dubin[14] the over-all pigment content was estimated as grade 3. Kupffer cells were more prominent than usual and occasionally projected into sinusoidal spaces. Many contained pigment granules identical with those seen in liver cells except that they tended to be smaller and of more uniform size. (Fig. 5.) The pigment content of Kupffer cells roughly paralleled that of adjacent liver cells in keeping with the general centrolobular arrangement already noted. A few fatty cysts were found in the central zone of lobules; these were enclosed by a thin rim of cytoplasm which contained the usual brown pigment. (Fig. 6.) Scattered lymphocytes and pigment-laden macrophages were present in portal areas.

HISTOCHEMICAL FINDINGS

All studies were carried out on paraffin tissue sections cut at 6 microns. The pigment under

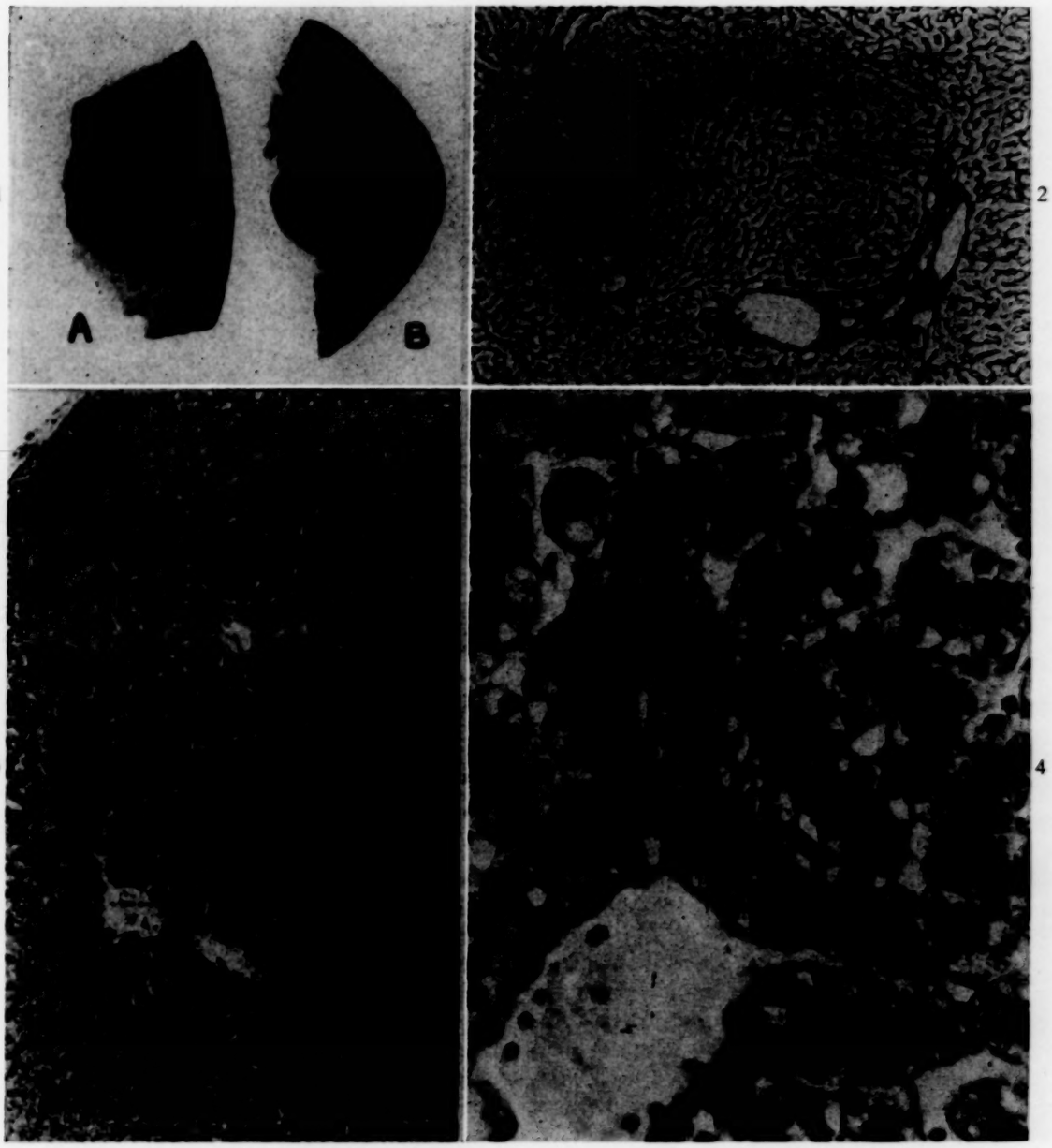

FIG. 1. Liver biopsy specimen (B) following formalin fixation, showing pigmentation of parenchyma as compared with the normal (A); × 3.8.

FIG. 2. Reticulum fibers have a regular pattern and are not thickened or increased in number; modified Foot's silver stain, × 50.

FIG. 3. Characteristic centrolobular distribution of pigment. Lobular architecture is not disturbed; Schmorl's ferric ferricyanide method for lipofuscin, × 66.

FIG. 4. Massive accumulation of coarse, granular pigment within liver cells surrounding a central vein. There is no evidence of necrosis, regeneration, inflammation or fibrosis; periodic acid-Schiff reaction, × 420.

consideration gave negative reactions with the Gmelin test for bilirubin and Perls' method for iron. It proved resistant to prolonged treatment with a wide variety of non-polar and polar solvents including alcohols (methyl, ethyl, butyl, isopropyl), ether, chloroform, acetone, xylene, benzene, dilute acids (hydrochloric, sulfuric) and alkalis (3 per cent potassium hydroxide, 10 per cent sodium hydroxide, concentrated ammonium hydroxide). The pigment

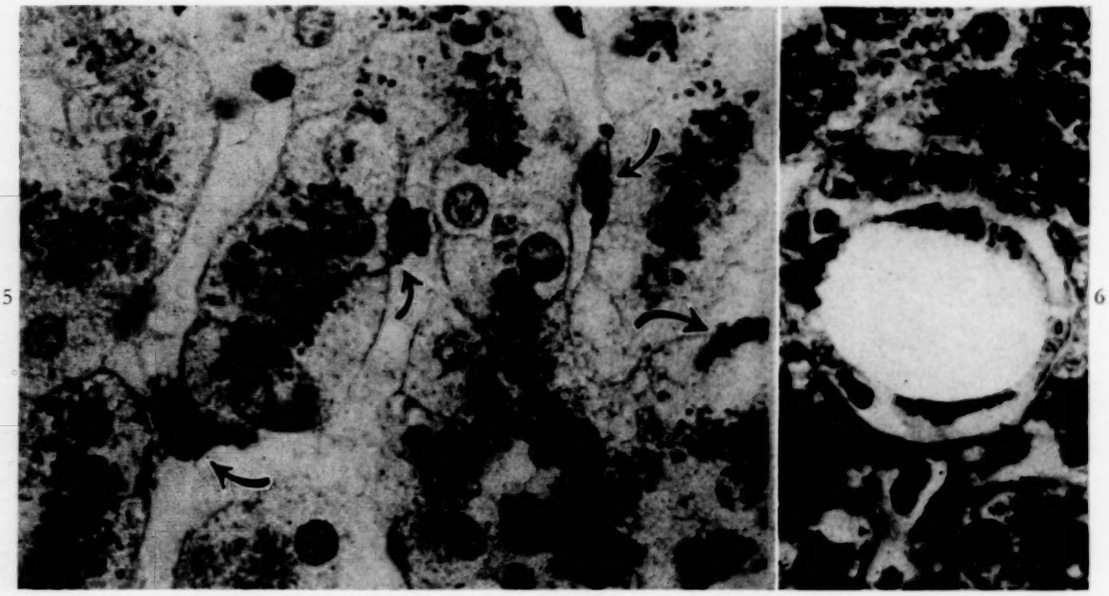

FIG. 5. Kupffer cells (indicated by arrows) are laden with deeply basophilic pigment granules. In adjacent liver cells, however, cytoplasmic pigment shows a variable staining reaction; Terry's methylene blue, × 800.

FIG. 6. Fatty cyst surrounded by a thin rim of cytoplasm containing pigment; periodic acid-Schiff reaction, × 800.

was isotropic under the polarizing microscope. Exposure to ultra-violet light excited a faint dull brown fluorescence. It lacked acid-fastness but this depended to some extent on the manner in which the Ziehl-Neelsen test was performed and interpreted. Pigment granules in paraffin sections were deeply stained by prolonged immersion in alcoholic Sudan black B solution. There was negligible affinity for Sudan IV, however, under similar conditions. With the periodic acid-Schiff method, granules were stained uniformly reddish brown. (Fig. 4.) This was in contrast to the bright red color of scattered deposits of glycogen, which were also visualized. In our hands the Feulgen method gave a faint reaction only with some of the smaller granules. Treatment with 5 per cent silver nitrate at 60°C. for two hours blackened many pigment particles, particularly those in Kupffer cells. With diamine silver hydroxide reduction was rapid and uniform. Schmorl's ferric ferricyanide method stained all the pigment dark blue. (Fig. 3.) This capacity to reduce ferric ferricyanide was abolished by oxidation for twenty minutes in 0.5 per cent potassium permanganate.

Strong basophilia was demonstrated with a variety of basic aniline dyes. When stained with basic fuchsin, the granules proved moderately resistant to decolorization with alcohol. With the Gram reaction crystal violet was retained, apparently on a similar basis. Deep coloration, with a trace of metachromasia in smaller particles, was achieved with Schmorl's thionine stain. Pigment in Kupffer cells was colored bright blue with Giemsa stain; in contrast, the same material in adjacent liver cells took the dye in a capricious manner and appeared bluish green. A similar tinctorial reaction was obtained with Terry's methylene blue. (Fig. 5.)

Treatment of sections with 0.25 per cent potassium permanganate (for ten minutes) followed by 5 per cent oxalic acid (for five minutes) resulted in complete destruction of the pigment. This was confirmed by darkfield microscopy and by negative diamine silver and periodic acid-Schiff reactions. However, application of Mallory's phosphotungstic acid hematoxylin revealed pale orange, ghost-like outlines of granules formed of protein matrix. Spherical and rod-shaped mitochondria, also demonstrated by this method, were present in normal numbers. A transition of mitochondria to pigment particles could not be demonstrated.

COMMENTS

The clinical features in our case were in close conformity with those reported by previous

authors.[14–16] The disease had its onset during early adult life. The initial phase bore some resemblance to infectious hepatitis but was gradually replaced by low grade jaundice which persisted for five years without incapacitation. Indeed, as in Gilbert's disease, our patient was usually "more icteric than sick." Nevertheless, coincident with episodes of increased jaundice, distressing symptoms such as blackouts, lassitude, vomiting, dizziness and right upper abdominal pain would make their appearance. Our case, apparently unlike others, was complicated by alcoholism, with recurrence of symptoms and increase in jaundice occurring in relation to prolonged bouts of drinking. During hospital admissions, with the withdrawal of alcohol and institution of bedrest and a high protein and vitamin diet, serum bilirubin levels always fell but never reached the normal range. Occasional fatty cysts found in the liver biopsy specimen were considered as evidence of previous fatty infiltration which had responded to adequate diet.

The only objective findings of significance were scleral icterus, slight hepatomegaly and liver tenderness. Serum bilirubin levels showed considerable fluctuation. Unlike Gilbert's disease, the hyperbilirubinemia was characterized by a high direct serum bilirubin which usually formed more than 50 per cent of the total. We have no adequate explanation for the mechanism whereby direct bilirubin accumulates. Dark urine, which contained bile and an excess of urobilinogen, was passed at intervals. Hemolytic jaundice was effectively ruled out by the completely normal blood findings and absence of splenomegaly. Dubin and Johnson[14] have shown that liver function tests such as bromsulphalein excretion, cephalin-cholesterol flocculation and thymol turbidity often give abnormal values in this disorder. The results of these tests in the present case, however, were consistently within normal limits. Although cholecystography was generally unsatisfactory, in our case there was some opacification of the organ following a double dose of radiopaque dye. As in previously reported cases,[14] exploratory laparotomy was performed in an effort to establish a diagnosis. The procedure served to exclude obstructive biliary disease, and indirectly assisted in diagnosis.

The outstanding anatomic finding confirming the diagnosis was the presence of coarse, granular, brown pigment within liver cells which imparted a greenish black color to the gross biopsy specimen. The pigment had a centrolobular distribution suggesting the existence of a metabolic gradient within lobules. Although diagnoses of chronic viral hepatitis and cirrhosis had been entertained on clinical grounds, confirmatory histopathologic evidence was lacking. The presence of pigment within the Kupffer cells, noted by Sprinz[15] but denied by Dubin,[14] is worthy of comment. In our material pigment within the Kupffer cells roughly paralleled the centrolobular distribution found in adjacent liver cells. The accumulation of pigment within liver cells is probably the result of an enzyme deficiency or block. It seems likely that as an alternative means of elimination the pigment is extruded from liver cells and phagocytosed by Kupffer cells, where it undergoes metabolic degradation. A supporting thread of evidence for this hypothesis is the enhanced staining, by several methods, of pigment within these phagocytic cells.

Dubin and Johnson[14] have considered the conspicuous hepatic pigment associated with the disorder to be a lipochrome-like substance or possibly a dipyrrolic compound such as mesobilifuscin. A number of insoluble, granular, iron-free pigments have been described as occurring in liver cells in health and disease, Some, such as lipofuscin,[17,18] hemofuscin (cytolipochrome)[19] and ceroid,[20] have been given a name, while others[14,21] are known only by their properties. We are of the opinion that the pigment in Dubin-Sprinz disease should be classed with the family of lipogenic pigments (lipofuscins) in view of its centrolobular distribution, physical properties and histochemical reactions.

Borst originated the term "lipofuscin" because he thought it was derived from some sort of lipoid.[22] Various other terms, such as waste pigment, brown atrophy pigment, wear and tear pigment, Abnutzungspigment and lipochrome (in American literature) have also been used to designate this somewhat heterogeneous group of endogenous pigments which are often found in heart muscle, liver cells, ganglion cells, adrenals, seminal vesicles and testes.[17] These iron-free, granular, yellowish brown pigments are basophilic, acid-fast, exhibit brown fluorescence, and reduce ammoniacal silver and Schmorl's ferric ferricyanide. They resist fat solvents but often stain with fat-soluble dyes even after paraffin embedding. Except for acid-fastness, identical properties were displayed by the pig-

ment in our material. Thus the relationship of lipofuscin to Dubin-Sprinz disease is characterized by its constant occurrence and striking abundance, rather than by a unique chemical constitution. Pearse[18] believes that lipofuscins are formed by oxidation from lipid precursors. Pigmentation, sudanophilia, basophilia, insolubility and reducing capacity apparently depend on the degree of oxidation as well as the nature of the original lipid and its protein content. Chemical identification of lipofuscin pigments has been hampered by their insolubility. The physical method for separation of ceroid described by Endicott and Lillie,[20] however, may prove applicable in this regard. Available evidence would indicate that these pigments are polymerized unsaturated fatty acids with free acid and reducing groups. Our findings suggest that the granules also contain a protein matrix. It is of interest that lipofuscins in different organs show considerable variability in staining properties.[17] Even at the same site within a section the individual granules of lipopigment may differ both in appearance and reaction.[18,22] This was also observed from our own material. For these reasons, when assessing histochemical findings, we placed greater reliance on general attributes than on minor variations with individual special stains.

Lipofuscin in liver cells has long been considered a waste product which accumulates in dust-like particles in old age, as well as in association with debilitating diseases such as tuberculosis or cancer. This view has recently been challenged by Bachmann.[23] In a study of 712 liver biopsy specimens (from 562 persons) he found that the quantity of lipofuscin depends only within certain limits upon age; a large quantity may be found in young people and none at all in old people. The formation and destruction of lipofuscin appears to be a function of normal liver cells, since repeat biopsy specimens taken after an interval of several months, from cases without hepatic disorder, showed considerable alteration in pigment content.

The fundamental nature of Dubin-Sprinz disease is unknown at present. On the basis of available knowledge it seems likely that there is an inborn or acquired error of metabolism of liver cells. Whereas in Gilbert's disease the metabolic disturbance appears to be confined to the excretion of bilirubin, in Dubin-Sprinz disease it is more widespread, as reflected by hyperbilirubinemia (with a large direct reacting component), accumulation of lipofuscin pigment in liver cells, delay in excretion of bromsulphthalein and radiopaque dyes, and abnormal results with serocoagulation tests. As in Gilbert's disease intercurrent illness may act as a precipitating or aggravating factor.[14] Our case demonstrates that chronic alcoholic overindulgence has a similar effect. Prolonged "hangovers" described in the protocol were considered further indication of impaired liver function. Although a total of fifteen reported cases are presently available for analysis, a familial pattern to Dubin-Sprinz disease has not been demonstrated.[14–16] Dubin and Johnson[14] have speculated that the disorder may be due to a decrease in liver catalase which permits the production of dipyrrolic compounds such as pentdyopents. The solution of this problem awaits further definitive investigation. To date there have been no reports of autopsied cases.

The clinicopathologic entity under consideration merits a convenient name for popular usage. We have proposed the term "constitutional non-hemolytic jaundice with 'lipochrome' hepatosis" as one which embraces the clinical picture and laboratory findings of the complaint. The shorter eponymic title "Dubin-Sprinz disease" serves equally well, providing its meaning is made clear by context.

Persons with the disorder are able to carry on their full activity during remissions of jaundice. Whether this indicates an excellent prognosis is not known, but such would appear to be the case. The most useful therapy one can give a patient, until the pathogenesis and definitive treatment of this disease are elucidated, is a diagnosis. This is of benefit because it prevents an erroneously serious prognosis and obviates unwarranted surgical treatment.

SUMMARY

An additional case is reported of a new clinicopathologic entity which has recently been described by Dubin and Johnson, and Sprinz and Nelson as "chronic idiopathic jaundice with unidentified pigment in liver cells." The evolution of the literature on the subject is traced, and a comparison with Gilbert's disease is offered.

The disorder is attributed to an error in liver metabolism. Alcoholism and intercurrent illness may act as precipitating or aggravating factors. Clinical features include persistent, low grade, non-hemolytic jaundice, lassitude, upper ab-

dominal pain and slight enlargement and tenderness of the liver. Direct reacting bilirubin is elevated and forms a major portion of the total. Bilirubinuria, abnormal serocoagulation tests, delayed bromsulphthalein excretion and failure to see the gallbladder on cholecystography may be demonstrated on occasion. The patient's general health is not impaired, and prognosis appears to be good.

A constant and diagnostic histologic finding is the presence of coarse, brown lipofuscin pigment within pericentrally placed liver cells. Histochemical reactions which permit characterization of this pigment are outlined and discussed.

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ACTH Therapy of Pituitary Failure*

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FAILURE of anterior pituitary function, with secondary thyroid, adrenal and gonadal hypofunction, has been the subject of considerable study in recent years.[1–3] The availability of adrenocorticotrophin has resulted in its use therapeutically in this disease although end-organ preparations (cortisone, testosterone, desoxycorticosterone and thyroid), used singly or in combinations, have been considered more efficacious. Some observers agree that ACTH therapy will produce a remission in pituitary failure but various objections have been expressed, such as the development of resistance to ACTH, the expense of injectable ACTH as compared with cortisone which is given orally, and the possibility that the clinical response to ACTH is inferior to cortisone.[4,5] A review of the literature reveals that ACTH has not been used frequently in this disease, although when adequate dosage was administered the response seemed to be good.[6–9]

The case to be described illustrates not only the excellent response which can be obtained with prolonged ACTH therapy in pituitary failure but also some of the diagnostic and theoretic aspects of this disorder. The methods usually employed in this laboratory were used in the endocrine evaluation of this patient.[10] The ACTH test involved intramuscular administration of ACTH over a period of forty-eight hours, and has been described elsewhere.[11]

CASE REPORT

C. O. B. (Ch No. I 50-403001), a sixty-one year old white man, was admitted to Charity Hospital in New Orleans on February 23, 1950, complaining of weakness.

About seventeen months prior to admission, while living in Chicago, he experienced an attack characterized by headache and nausea followed by weakness. Weakness, mild anorexia, occasional nausea, vomiting and gradual loss of weight continued although he was able to maintain a sedentary occupation. One month later rather severe nausea and vomiting developed; this was unaccompanied by pain but resulted in extreme weakness for which he was hospitalized. He was told he had severe anemia, probably due to a malignant tumor. During this period his weight decreased from 158 to 142 pounds. He was unaware of any changes in the skin, hair or nervous system.

In January, 1949, abdominal exploration failed to reveal any disease. The postoperative period was uneventful. The patient was discharged from the hospital three weeks later with a neuropsychiatric diagnosis. The mild weakness, nausea, headache and occasional vomiting continued.

Because of increased sensitivity to cold, despite warm clothing and housing, he moved South. While in New Orleans he first noticed increased dryness and coarseness of his skin along with noticeable loss of axillary and pubic hair. The weakness was severe enough to prevent working. Shaving was necessary only three times weekly rather than daily, as prior to the onset of his illness. The penis and testes became smaller and libido decreased. Constipation developed about one month before hospital admission. Mental alertness was definitely reduced and speech was slurred and slow. At no time had he had any symptoms suggestive of cardiac, respiratory or urinary disease. The weakness became progressively worse and he reported to the hospital for admission.

On admission to Charity Hospital, New Orleans, physical examination revealed an elderly, thin, apparently chronically ill man with pale, dry, coarse, wrinkled skin. (Fig. 1.) There was no evidence of increased cutaneous pigmentation. The axillary and pubic hair was sparse. He was somewhat hoarse, spoke slowly and responded to questioning poorly. He weighed 124 pounds (height, 67¾ inches). Blood pressure was 90 mm. Hg systolic and 50 mm. Hg diastolic. Temperature, pulse and respiration were normal. The conjunctivas and retinal fundi were pale but otherwise normal. A midline abdominal non-pigmented scar, well healed, was present. The testes were soft and small, and the penis appeared normal. Rectal examination revealed no prostatic enlargement. Muscle tone of the entire body was poor. Examination of the deep tendon reflexes revealed a good,

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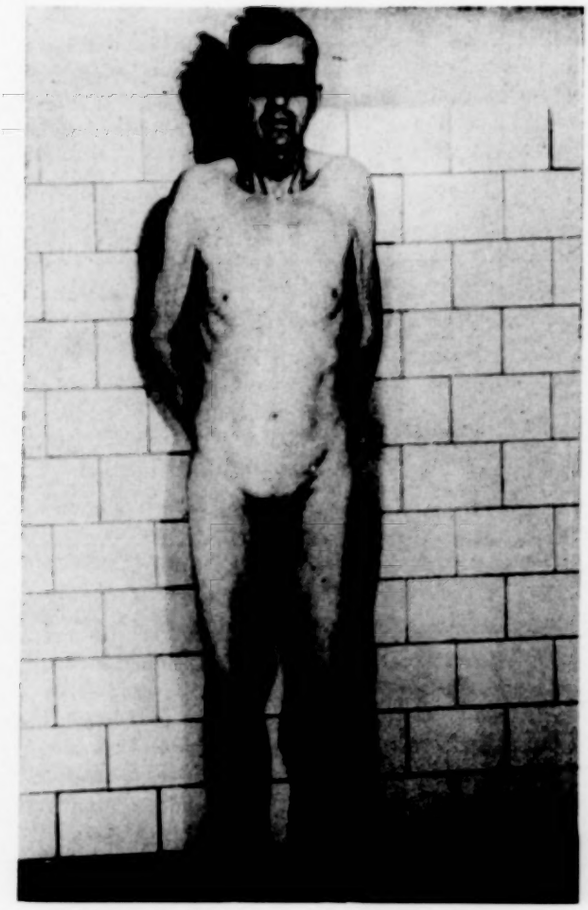

FIG. 1. No therapy (April 26, 1950).

quick muscle response but with slow return to the resting stage, which is so characteristic of myxedema.[12] The remainder of the physical examination was normal.

The red blood cell count was 3,560,000 per cu. ml. with 10.9 gm. hemoglobin per 100 cc., a hematocrit of 35 per cent and a normal white blood cell count. The sedimentation rate (Wintrobe) was 56 mm./hour uncorrected. The result of sternal bone marrow examination was normal. Urinalysis revealed an acid urine with specific gravity of 1.019, no albumin and a normal sediment. Blood cholesterol was 550 and 314 mg. per cent, respectively, and the serum protein was 5.8 gm. per cent with normal albumin and globulin. Blood urea nitrogen, calcium, phosphorus, alkaline and acid phosphatase values, as well as liver function studies, were within normal limits. The basal metabolic rates on two occasions were −18 per cent and −13 per cent, respectively; this was considered normal for the Gulf Coast area. A glucose tolerance test showed a mildly hyperglycemic response. Gastric analysis revealed no free acid with a total acid of only 20 per cent. Fecal examinations repeatedly failed to disclose blood or parasites. Roentgenography of the entire gastrointestinal tract, chest, spine, skull and long bones failed to reveal any significant abnormalities. An electrocardiogram showed a low QRS complex in lead I and a low T wave in lead III. The visual fields were normal. Spinal fluid examination revealed no abnormalities. Serologic reactions for syphilis were

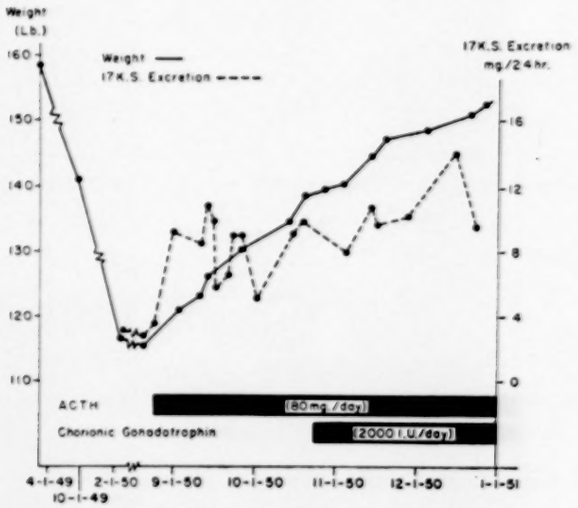

FIG. 2. Weight and 17-ketosteroid response to therapy.

negative in both spinal fluid and blood. An epinephrine test for hypothalamic-pituitary-adrenal function revealed a decrease in blood circulating eosinophils of only 28 per cent from the control level of 322 cells per cu. ml. A Robinson-Power-Kepler test for adrenal insufficiency yielded a positive result with a numerical index of 8. A forty-eight-hour intramuscular ACTH test indicated a delayed adrenal response in which a significant eosinophil and 17-ketosteroid change occurred, but not until forty-eight hours after the ACTH had been administered.

Since the adrenal was capable of stimulation by ACTH it seemed reasonable to assume the presence of primary pituitary failure with secondary adrenal insufficiency. The diagnosis of pituitary failure was made on the basis of clinical evidence of myxedema, adrenal insufficiency and hypogonadism. The finding of the myxedema reflex, a 17-ketosteroid excretion of 2.5 mg./twenty-four hours and a gonad-stimulating hormone assay of less than 6.6 mouse uterine weight units confirmed each of the clinical findings, respectively.

During the entire period of diagnostic study the patient was confined to bed and given a high protein, high carbohydrate diet supplemented by intravenous administration of fluids as needed. Upon completion of these studies intramuscular testosterone propionate (25 mg. daily, with and without 2.5 mg. of desoxycorticosterone) was tried. Nausea and weakness increased following testosterone therapy. Aqueous adrenocortical extract intramuscularly and glucose

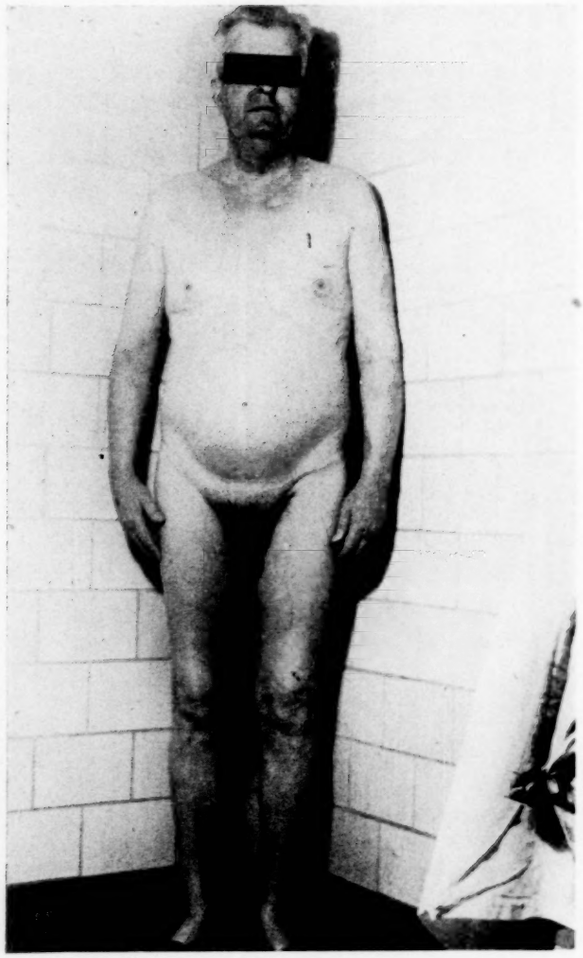

FIG. 3. After ACTH therapy (May 16, 1951).

and saline intravenously were the only medications which definitely produced clinical improvement.

It was then decided to try ACTH therapy. On August 23, 1950, administration of ACTH (lyophilized) was begun in intramuscular doses of 20 mg. every six hours. Within three days the patient was again able to walk, was in better spirits, appeared rather alert and had such an increase in appetite that he frequently requested double portions of food. The clinical course steadily improved. Gain in weight was constant. (Fig. 2.) Blood pressure returned to normal. Although the skin lost its wrinkled appearance and regained its elasticity, the dryness and coarse texture remained.

It was decided to determine whether any added benefit might result from combining chorionic gonadotrophin with ACTH therapy. Histologic examination of the particles on October 3rd showed complete atrophy of the interstitial as well as tubular elements. On October 23rd, daily intramuscular injection of 2,000 international units of chorionic gonadotrophin was begun. Changes in urinary hormonal excretion are shown in Figure 2 and Table I. Following this the patient showed continued improvement except for a mild episode of weakness due to potassium deficiency in November which responded within twenty-four hours to oral administration of potassium citrate. While receiving combined therapy the patient noted the development of a much coarser beard, some

TABLE I

URINARY EXCRETION IN PITUITARY FAILURE

Therapy	17-Ketosteroids (mg./24 hr.)	Formaldehydogenic Corticoids (mg./24 hr.)	Gonad-stimulating Hormone (mouse uterine wt. units)
None	2.5(4)*	0.04(2)	<6.6(1)
ACTH	7.68(16)	0.66(6)	<6.6(1)
ACTH and chorionic gonadotrophin	10.18(7)	0.50(4)	>480(3)

* Numbers in parentheses represent number of separate determinations performed.

enlargement and increased firmness of the testes, penile erections and, on several occasions, nocturnal emissions. Roentgenograms of the skull and spine in December revealed no evidence of osteoporosis. Histologic examination of the testicles on February 1, 1951, revealed slight stimulation of the Leydig cells compared with the previous biopsy. Other laboratory data obtained at this time showed, in general, little change from those obtained previously. There was a slight increase in hemoglobin and serum protein. The results of the glucose tolerance test again showed a slight hyperglycemic response, with elevated blood sugar in the third hour specimen. In March, 1951, the protein-bound iodine was 3 μg./100 cc. serum and the I-131 uptake was 61 per cent in twenty-four hours. There was no evidence of axillary hair development while the patient was receiving ACTH alone or when combined with gonadotrophin therapy.

Chorionic gonadotrophin therapy was discontinued in March, 1951. From then until October, 1952, the patient received ACTH in various available preparations by different parenteral routes. During this period the 17-ketosteroid excretion varied from 2 mg./twenty-four hours to 18.8 mg./twenty-four hours depending upon the dose and route of administration. His slightly cushingoid but otherwise normal appearance can be seen in Figure 3, taken May 16, 1951. In October, 1952, the patient was discharged from the hospital. He was instructed to take 15 units of ACTH HP gel once daily intramuscularly. When seen on March 31, 1954, the patient was taking 14 units of ACTH HP gel per day. His weight was 170 pounds, and except for some generalized weakness, his health continued to be good. The 17-ketosteroid excretion at this time was 4.3 mg./twenty-four hours and the formaldehydogenic corticoid excretion was 0.6 mg./twenty-four hours. Blood chemical studies yielded

normal values. The dosage of ACTH HP gel was increased to 18 units per day and maintained at that level.

COMMENTS

Albright, Forbes and Bartter[13] suggested that two adrenocorticotrophic hormones might be necessary for the production of androgen from the adrenal. They pointed out that in girls adequate "S" hormone is produced, as evidenced by resistance to fasting and absence of Addisonian crisis, yet no androgen is produced. At puberty, urinary excretion of 17-ketosteroid begins and this is associated with the development of axillary and pubic hair at the time of ovulation. Both the ovulation and the apparent initiation of androgen production by the adrenal are ascribed to the production of LH from the anterior pituitary.[13] In a series of three patients with panhypopituitarism treated with ACTH, Bartter and others[14] found only one who showed a rise in 17-ketosteroid excretion. In this patient a testicular biopsy showed evidence of LH stimulation. This suggested that ACTH produces less rise in 17-ketosteroid excretion in a patient with pituitary failure than in a normal person, because of the absence of LH necessary for adrenal androgen production. Talbot and associates[15] have shown that the adrenal in the child can respond to ACTH if the ACTH was the same as that produced in the adult. This suggested the possibility of two types of adrenocorticotropic hormone.

As can be seen in Table 1, addition of gonadotrophin to ACTH in therapy resulted in the case reported herein, in an increase in 17-ketosteroid excretion while the cortin excretion remained unchanged. Also in the patient at this time there was convincing clinical evidence of androgen production not noted during ACTH therapy alone, namely, increased genital growth, penile erections and nocturnal emissions. It is interesting to note that while the patient received the single and combined therapy, axillary hair failed to develop. We can offer no good explanation for this although an end-organ defect is one possibility. The possibility that gonadotrophin was present in the ACTH preparation and that this was responsible for the increase in 17-ketosteroid excretion while the patient was receiving ACTH therapy alone is not tenable, since the method for preparation of the ACTH employed effectively destroys all the gonadotrophic hormone content. In addition, the first testicular biopsy specimen was taken while the patient was receiving ACTH therapy and it showed complete atrophy. While the patient was receiving combined therapy, the added androgen production which occurred was probably testicular in origin although the second biopsy specimen revealed only moderate changes in Leydig cell development. The possibility that addition of gonadotrophin to the ACTH resulted in increased androgen production from the adrenal is one that we consider extremely interesting in the light of Albright's hypothesis.

With regard to the diagnosis of pituitary failure in this patient, several points should be mentioned. The history of nausea, vomiting and weakness, associated with loss of weight, in the absence of any other specific complaints, is suggestive of pituitary failure. Decreased resistance to minor infections, associated with increasing nausea and vomiting during these periods, is frequently the complaint which brings the patient to the physician initially. Although the results of physical examination of patients with pituitary failure frequently appear to be relatively normal, certain points are of great help in making the clinical diagnosis. Absence of pigmentation in the skin of a patient thought to have adrenal insufficiency should suggest a pituitary rather than a primary adrenal origin. The yellowish, dry, scaly skin, which is somewhat coarse in character, and the presence of myxedema are pathognomonic of thyroid deficiency. The decrease (in many patients complete absence) of axillary hair further suggests adrenal insufficiency. The additional findings of small external genitals and small soft testes in the male, or atrophy of the breast and amenorrhea in the female, are good indications of hypogonadism. The combination of changes suggesting adrenal, thyroid and gonadal deficiency should indicate the diagnosis of pituitary failure. The possibility of a functional type of pituitary failure seen in anorexia nervosa and starvation should be considered but can usually be eliminated in consideration of the patient's history, age and psychologic evaluation.

Laboratory determinations of help in confirming the diagnosis were decreased pituitary gonadotrophin, decreased 17-ketosteroid excretion and the good response to the forty-eight-hour ACTH test. Protein-bound iodine determination would probably be of value, since the basal metabolic rate and blood cholesterol frequently are normal in pituitary failure. Because

it has been shown that primary thyroid myxedema may produce changes like those of pituitary myxedema the I-131 uptake test before and after administration of thyroid-stimulating hormone has been suggested as a means of ruling out this possibility.[16] The 61 per cent I-131 uptake during ACTH and gonadotrophin therapy indicates the functional potential of this patient's thyroid, probably in response to thyroid-stimulating hormone contained in the pituitary preparations used. The value of the forty-eight-hour ACTH test for adrenal function is emphasized by the fact that had only a four-hour test been performed in this patient, an unresponsive adrenal would have been assumed to be present, whereas actually it was responsive but simply required more prolonged stimulation.[11] It should be remembered that pituitary failure may be incomplete, without involvement of all trophic hormones. Such patients may have symptoms suggesting a deficiency of only one end-organ.

Few articles on pituitary failure in the literature describe prolonged treatment with ACTH. Brown and Greenblatt[4] thought that prolonged administration of ACTH induced a modified adrenal response and that the adrenal gland so stimulated could not be maintained at high levels of activity. Horrax and others[17] were able to obtain gratifying results with administration of ACTH in pituitary failure secondary to chromophobe tumors; however, because of sensitivity to ACTH or for other reasons, oral cortisone was used instead. McCullagh and co-workers[18] expressed the opinion of many others that consistently good results can not be predicted when ACTH is employed and, in addition, the slow response (as compared with the orally administered cortisone) is a distinct disadvantage. On the other hand, Maddock and associates[7] were able to obtain good results with prolonged ACTH therapy in daily dosages of 20 to 50 units of the aqueous preparation intramuscularly. They were unable to demonstrate an effect from chorionic gonadotrophin therapy in either of two patients receiving it. It is interesting that testosterone therapy elicited weakness, leg cramps and anorexia, which improved when ACTH was substituted for testosterone. This reaction was also noted in our patient, for reasons which are not clear to us. Ekholm[6] obtained good results with ACTH but mentioned the possibility that pituitary basophilic atrophy and ACTH overstimulation resulting in adrenal fatigue might occur. He considered a combination of ACTH and thyroid to be better therapy than ACTH alone. Rolland and Matthews[8] reported good results following a brief period of therapy with ACTH although migraine and hemiparesis occurred in one patient.

The data in Table 1 and Figure 2 indicate an excellent clinical response to ACTH in the case reported herein. It was disappointing at first that there was no response to testosterone and desoxycorticosterone. Why the response to testosterone is favorable in some patients and unfavorable in others is not clear.

During ACTH therapy the patient showed the expected sense of well-being in addition to improved hydration, appetite and physical stamina. The addition of chorionic gonadotrophin therapy had little effect on the patient's clinical response. He continued to gain weight, as he did when receiving ACTH alone; and the increased hair growth, as well as increased size and function of the genitals, were the most significant clinical changes seen during the combined therapy. In younger men there probably are indications for combined therapy but perhaps not in older men. Osteoporosis did not develop in our patient, as reported by Bartter and associates,[14] although the period of treatment was short at the time the second roentgenograms were taken. Electrocardiographic changes compatible with potassium deficiency during ACTH therapy suggest that supplemental potassium chloride therapy be given orally to patients receiving prolonged ACTH for pituitary failure.

SUMMARY

Prolonged administration of ACTH to a patient with pituitary failure resulted in an excellent subjective and objective response which has been maintained for three and a half years. Combined chorionic gonadotrophin and ACTH therapy did not have any advantage over ACTH alone in this patient.

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Neurologic Changes in a Patient with a Portacaval Shunt and the Relationship to Hepatic Coma*

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THE syndrome of disturbed mental function, flapping tremor and electroencephalogram changes associated with liver disease and known as hepatic coma[1] has long been considered due to toxins passing from the portal into the systemic circulation through an impaired liver. Likewise, the syndrome of "meat intoxication" occurring in dogs with an Eck fistula has been considered due to toxins being shunted directly from the portal into the systemic circulation. Strong evidence now exists that both conditions are due to ammonia intoxication, caused by ammonia formed in the gastrointestinal tract passing into the systemic circulation either through a severely damaged liver or through collateral channels. The following case report of a patient with an Eck fistula of five years' duration demonstrates this phenomena.

CASE REPORT

H. L. is a twenty-three year old Chinese man whose medical history began on Okinawa in 1949, when he had a sudden episode of hematemesis followed by shock. Physical examination showed hepatomegaly and splenomegaly; an upper gastrointestinal series demonstrated esophageal varices. At that time there was a pancytopenia with a platelet count of 27,000, a white blood cell count of 1,750, and a red cell count of 2.7 million. A diagnosis of Banti's syndrome was made. Diagnostic studies for schistosomiasis and other possible causes of Banti's syndrome were negative.

Following splenectomy pancytopenia subsided. Section of the spleen showed chronic passive hyperemia; a surgical biopsy specimen of the liver was reported as normal. Flocculation tests gave negative results and bromsulfathalein retention was less than 3 per cent.

The patient was returned to the United States where he had two more episodes of hemorrhage with shock. Again, esophageal varices were demonstrated. In May, 1950, an end-to-side portacaval anastomosis was performed at the Letterman Army Hospital. The initial portal pressure was 360 mm. of water and the postoperative pressure was 16 mm. of water. On gross examination the liver appeared normal; a surgical biopsy specimen showed normal liver tissue with a possible slight increase in connective tissue on microscopic examination. Liver function tests were within normal limits.

Following this operation the patient was well for about six months; burning epigastric pain then developed. X-ray of the gastrointestinal tract revealed a scarred, deformed duodenum but no evidence of esophageal varices. There were multiple hospital admissions from 1951 to 1954 for epigastric pain; the duodenal deformity was consistently noted on x-ray. The liver was not palpable during these admissions and liver function tests remained within normal limits. During these hospitalizations it was noted that the patient's attitude varied from pleasant cooperation to dull apathy or sufficient belligerence to necessitate his being placed on the locked ward. In July, 1954, subtotal gastrectomy was performed because of intractable pain; the immediate postoperative course was uneventful.

One month postoperatively the patient returned to the hospital complaining of "difficulty in seeing." He was noted to have a marked stammer, a staggering gait, a coarse tremor of his hands and some mental confusion. Eyegrounds and visual fields were within normal limits. The only other neurologic findings were absent corneal reflexes. The liver was not palpable. Laboratory tests, including liver function tests, were within normal limits. A tentative diagnosis of conversion reaction or possible schizophrenia was made.

The hospital course over the next two months is outlined in Figure 1. The patient became more mentally confused and the tremor more marked; there was one episode of frank coma. The organic nature of the disease was demonstrated by a grossly abnormal electroencephalogram. Because of this and a recent article by McDermott[2] describing similar

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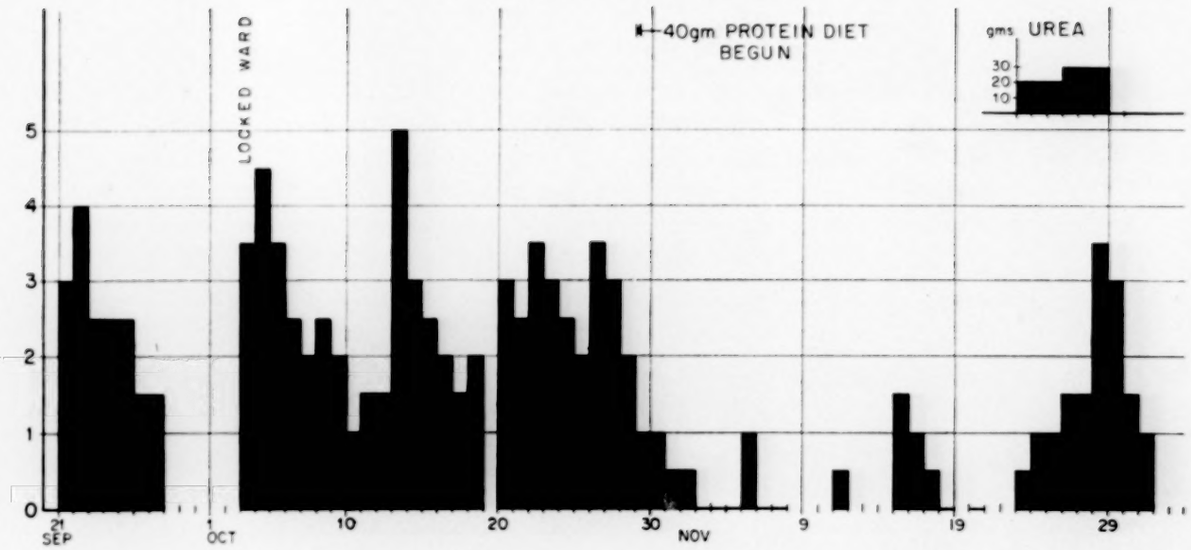

FIG. 1. Hospital course showing prompt disappearance of symptoms while the patient was on protein restriction therapy (October 29), recurrence of symptoms when urea was added to diet (November 23). (Days which lack any marking represent times during which notes about patient's mental status were inadequate to draw any conclusions.) Note: 0 = normal; 1 = slightest mental change; 2 = more marked, irritable; 3 = very marked tremor, aggressive, stammers severely; 4 = completely disoriented; 5 = coma.

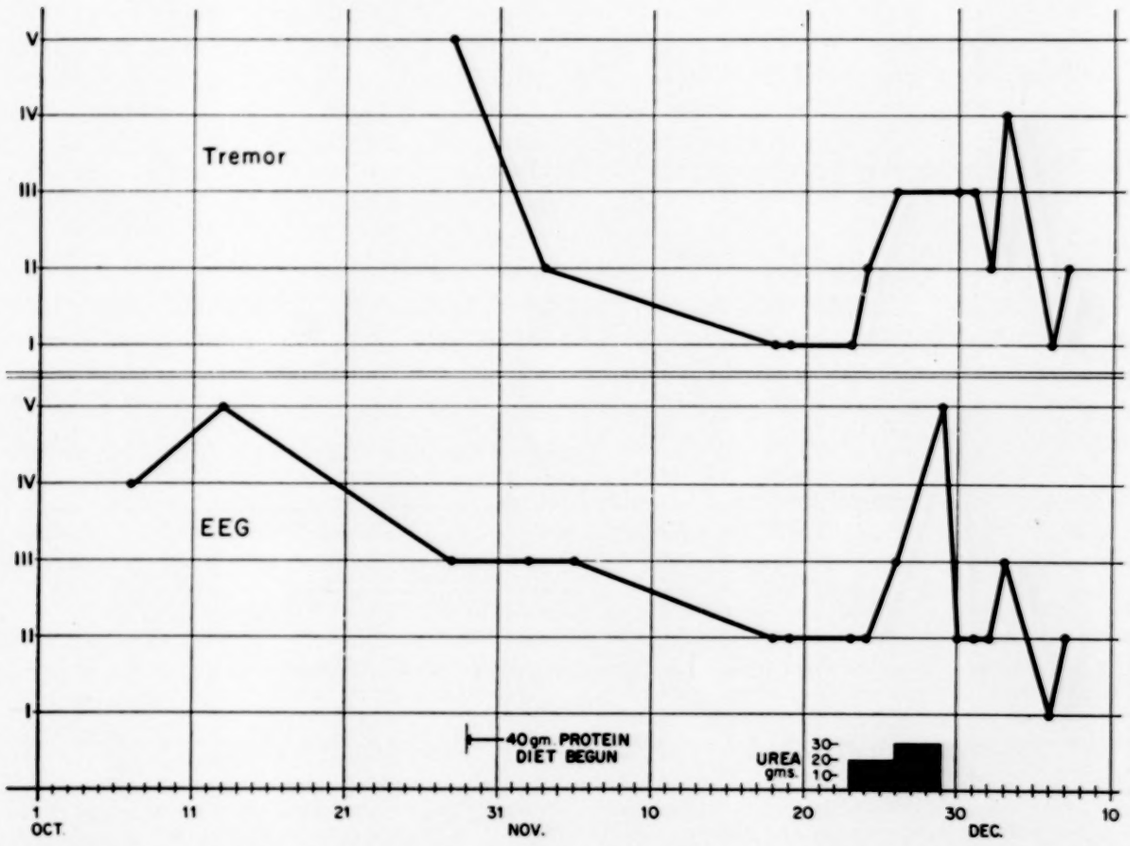

FIG. 2. Alterations in electroencephalogram and tremor with change from most abnormal (grade v) to normal (grade i) on protein restriction, and reversion to abnormal pattern on addition of urea.

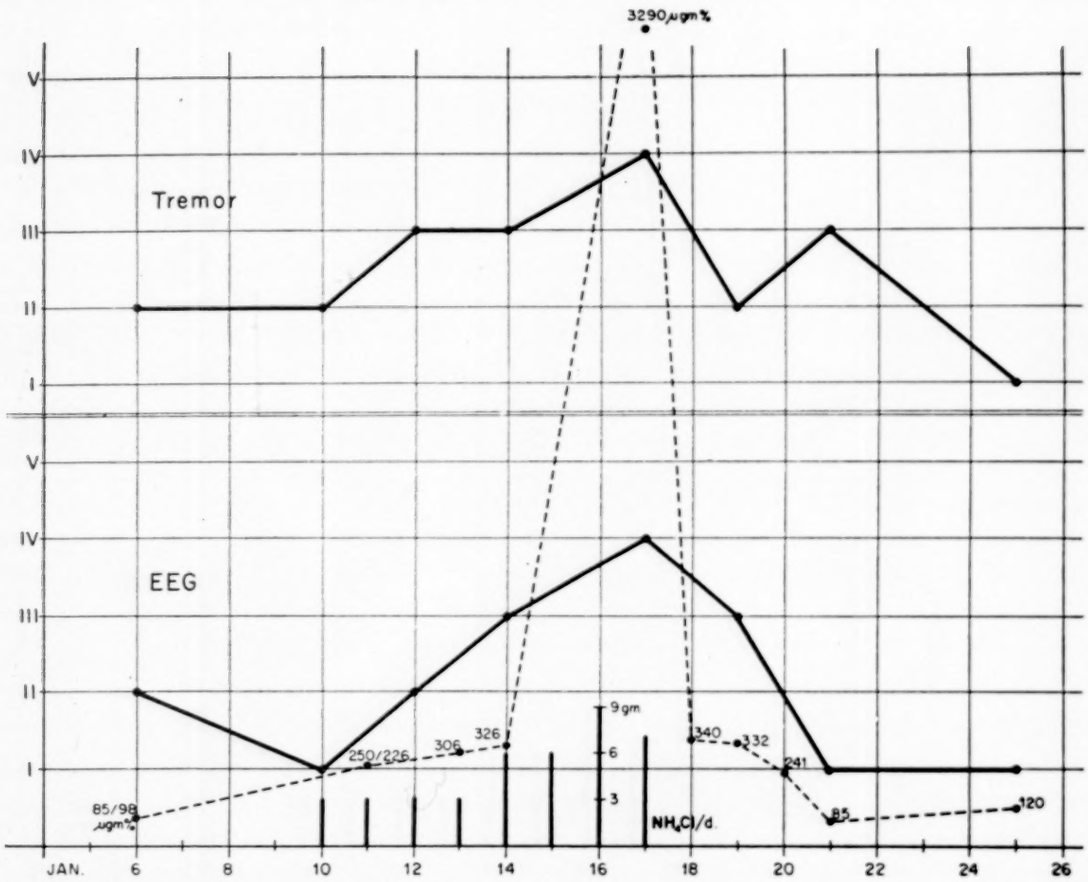

FIG. 3. Alterations in electroencephalogram and tremor with ingestion of ammonium chloride while patient received a 40-gm. protein diet, correlative with serum ammonia levels.

attacks of "episodic stupor" due to ammonia intoxication in a patient with an Eck fistula, a low protein diet (40 gm. protein) was instituted, with dramatic disappearance of symptoms over a four-day period. The patient became alert, docile and cooperative. (Fig. 1.) His postural tremor and visual complaints subsided and the electroencephalogram became normal. (Fig. 2.)

In order to prove the concept of ammonia intoxication, two provocative tests were performed. After a control period on a 40-gm. protein diet during which frequent electroencephalograms and tremograms were taken and the patient's mental status and behavior pattern noted, 20 gm. of urea and then 30 gm. of urea were added to the control diet for six successive days. By the first day slight mental changes and irritability had developed. The tremor appeared the second day and was marked by the third day; the electroencephalographic changes closely paralleled the clinical changes. (Fig. 2.) By the fifth day the patient was very uncomfortable; the urea was discontinued on the sixth day with prompt disappearance of symptoms and return of the tremogram and electroencephalogram to normal.

A second provocative test was carried out one month later with a control 40-gm. protein diet. Blood was drawn from the antecubital vein of both the patient and a normal control subject and the serum ammonia determined immediately by a modified Conway method. During the control period the patient's serum ammonia levels varied from 85 to 98 μg./100 cc.; the normal controls always ranged from 22 to 87 μg./100 cc. The patient was then given ammonium chloride, 3, 6 or 9 gm. over an eight-day period, with prompt return of confusion, irritability, tremor and electroencephalographic changes. These correlated with a serum ammonia level rise to a peak of 3,290 μg./100 cc. (Fig. 3.) Discontinuance of the ammonium chloride was coincident with a rapid drop in serum ammonia, disappearance of the symptoms and of changes in the electroencephalogram and tremogram.

The patient has done well and remained asymptomatic for over a year on a 40-gm. protein diet. The cephalin flocculation test is 2 plus and thymol turbidity is 3 plus. One bromsulphthalein test showed 15 per cent retention but the remainder were less than 3 per cent.

ELECTROENCEPHALOGRAPHIC AND POSTURAL TREMOGRAM CHANGES

Frequent electroencephalograms were obtained. They were arbitrarily divided into five groups from normal (1) to most abnormal (v). The most abnormal were characterized by moderate voltage, diffuse 2 to 3/sec. (delta) waves with some scattering of 4 to 6/sec. (theta) waves. The delta activity waxed and waned but no distinct paroxysmal activity similar to that described by Adams[1] was seen. The slowing was synchronous bilaterally and had a higher amplitude anteriorly than posteriorly. The amount of alpha activity was inversely proportionate to the amount of theta which in turn was inversely proportionate to the amount of delta. Particular attention was paid to the presence of triphasic sharp wave activity because of the description of such activity in patients with hepatic coma.[3] Poorly defined sharp wave activity was not noteworthy in any of the records except in one record obtained when the blood ammonia had reached a peak of 3,290 μg. (January 17). For the most part the records were indistinguishable from other severe encephalopathies such as that associated with hypoglycemia. The lowest level of blood ammonia which corresponded to the first changes toward abnormal in the electroencephalogram in this patient and another patient, not described here but who had about the same problem, was between 200 to 350 μg./100 cc.

Measurement of the patient's postural tremor was also obtained at regular intervals.[4] Again, the recordings were arbitrarily divided into five groups from normal (1) to most abnormal (v). The most abnormal was characterized by an irregular 4 to 5/sec. frequency with considerable superimposed 9 to 12/sec. frequencies. The slow characteristics became more prominent the longer the patient held his hands extended. As with the electroencephalogram, the critical level of blood ammonia which corresponded to the appearance of an abnormal tremor was about 200 to 350 μg./100 cc. There was the suggestion that changes in tremor may have preceded electroencephalographic changes and then this abnormal tremor may have persisted for a slightly longer time than the abnormal electroencephalogram.

COMMENT

Eck performed the first portacaval shunt in a group of dogs in 1877 and concluded from his short observation of these animals that "the blood of the portal system could, without any danger to the body, be diverted into the systemic circulation by means of a perfectly safe operation."[5] Experimental interest in the operation continued and in 1893 Hahn et al.[6] reported the occurrence of neurologic symptoms in dogs with portacaval shunts after ingestion of meat. In 1932, Balo and Korpassy[7] reported that "'meat intoxication' of dogs with Eck's fistula resulted in a syndrome of lethargy, weakness, excessive salivation, hypotonia, ataxia, amaurosis, stupor, convulsions and sometimes death." These and other observers also noted elevated serum ammonia levels in dogs with "meat intoxication."[7,8]

In 1954 McDermott[2] reported a case of "episodic stupor" and an abnormal electroencephalogram in a patient with a normal liver and a portacaval shunt; in 1955 Havens[9] reported a case of severe liver disease and portacaval shunt in a patient who had an abnormal electroencephalogram and had psychotic reactions while receiving a high protein diet. Both of these patients had an elevated serum ammonia associated with the syndrome and both patients could be controlled by protein restriction.

Phillips et al.,[10] prompted by the observation that ammonium exchange resins often provoked neurologic symptoms in patients with liver disease, was able to produce a syndrome indistinguishable from impending hepatic coma in patients with chronic hepatitis without previous neurologic symptoms by administering ammonia-producing compounds. Kirk[11] had previously done a very comprehensive study on ammonia and amino acid metabolism and noted the correlation between elevated serum ammonia and neurologic symptoms. In his work, based on a group of chronic cirrhotics and experimental animals, elevated serum ammonia was found only in those with evidence of collateral circulation. He also noted that as much as 80 per cent of the liver could be removed from normal animals without the appearance of ammonia in the systemic circulation. He concluded that the neurologic syndrome accompanying liver disease was due to ammonia being shunted from the portal vein directly into the systemic circulation by means of collaterals, and that even a badly injured liver was able to metabolize ammonia if not bypassed. The work of Mann et al. at Mayo Clinic seemed to bear this out.[12] Dogs with livers extensively damaged by carbon tetrachloride readily re-

moved ammonia from the portal circulation but even small amounts of ammonia instilled into the gastrointestinal tract of dogs with Eck's fistulas could be found promptly in the systemic circulation. These workers also observed that an ammonia level approximately two and a half times normal and sustained for some hours was necessary before toxic symptoms appeared, but that brief transient rises did not produce symptoms. Sherlock et al.[13] found elevated ammonia levels in the hepatic veins of patients with fatal acute hepatitis and no collateral circulation, indicating that ammonia can pass through a severely damaged liver. They also observed that patients with chronic liver disease and collateral circulation had systemic ammonia levels higher than hepatic vein ammonia levels, substantiating the finding that chronically damaged livers were able to metabolize ammonia but that it freely entered the peripheral circulation through collaterals.

It seems apparent that ammonia, while not the sole cause of hepatic coma, can reproduce the syndrome when occurring in sufficient concentration in the systemic circulation. It has been shown that only minute amounts of ammonia are formed by kidney and liver, and that the significant mode of ammonia formation from urea is due to the urease activity of bacteria in the gastrointestinal tract.[14] Normally, this ammonia is converted through the ornithine cycle into urea by the liver. However, bypassing the liver through surgical or collateral shunts easily allows the build-up of significant systemic levels.

The mode of action of ammonia on the central nervous system remains unclear. There are those that believe it exerts a direct toxic effect on the brain cells; McDermott has stated that he believes he can correlate the syndrome with electroencephalographic and histopathologic changes in the brain.[15] Bessman and Fazekas have observed reduced oxygen uptake of the brain in patients with hepatic coma and increased ammonia uptake, and suggest that the ammonia may bring about a reduction in amination of ketoglutaric acid which forms glutamic acid in the Krebs cycle, thereby interfering with normal brain metabolism.[16]

These observations and concepts are of importance in considering the management of the postoperative patient with Eck's fistula and in the patient in or near hepatic coma.

SUMMARY

1. A patient with a portacaval shunt and neurologic and electroencephalographic changes simulating those of hepatic coma is described.

2. The syndrome was demonstrated to be completely controlled by protein restriction and to be precipitated by adding ammonia-producing compounds to the patient's diet.

3. The appearance of symptoms and electroencephalographic changes coincided with an elevation of serum ammonia in the systemic circulation and the disappearance of the syndrome coincided with a return of the serum ammonia to normal levels.

4. This case has been correlated with other work done on this syndrome and its significance is discussed.

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The Syndrome of Chronic Thrombosis of the Major Pulmonary Arteries*

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UNUSUAL forms of heart disease assume more than casual interest when their diagnosis becomes easier and prevention or treatment possible. For this reason chronic cor pulmonale resulting from thrombosis of the major pulmonary arteries merits increased interest. Recent progress in cardiology has made the diagnosis of this syndrome possible and its treatment feasible. Early diagnosis and treatment should save some patients with this syndrome.

In 1934 a review of the literature yielded only twenty-four case reports.[1] The clinical syndrome was characterized by dyspnea, cyanosis, pain in the chest and progressive failure of the right side of the heart. Most cases were a complication of mitral stenosis or were ascribed to arteriosclerosis of the pulmonary artery. In 1940 a collected series of twelve cases was added to the eighty-eight cases previously reported.[2] Additional clinical features included peripheral edema, weak pulse, low blood pressure and mental confusion. Men were more frequently affected than women. Almost half the patients were under fifty years of age. The syndrome was also found to be a frequent complication of fibrosing pulmonary diseases such as tuberculosis and silicosis. The right pulmonary artery was the site of thrombosis in all but six of the 100 patients and the left pulmonary artery was thrombosed in almost half. No antemortem diagnosis had been made up to that time.

This article reviews the American and European literature since 1941, during which period present concepts of this syndrome have evolved, and presents two additional cases. The latter illustrate different phases in the course of the condition. One case was diagnosed prior to death.

CASE REPORTS

CASE 1. W. J. D., a twenty-four year old office clerk, entered the Veterans Administration Hospital, San Francisco, on November 3, 1948, complaining of exertional dyspnea, weakness and palpitation. He had been well until three weeks prior to admission, at which time he noted the sudden onset of sharp pain in the lower left chest. This pain was aggravated by deep breathing and by lying on his left side. There were no other symptoms. He remained at partial bedrest for the next few days. He continued to have dyspnea on exertion and occasional mild pain in the chest. Five days after the onset of his illness he was seen by his physician. A chest film and electrocardiogram were taken and were reported as normal. He noted an occasional rise in temperature up to 101°F. One week prior to admission he was again seen by his physician. A second normal electrocardiogram was obtained. There was no history of recent infections, dental extractions or surgical procedures. He stated that he had lost five pounds in weight during the three weeks he had been ill. The recent history was otherwise negative.

In 1954 the patient had pneumonia which was treated with sulfonamides. He was a prisoner of war in Germany for seven months, during which time he was treated for malnutrition and scabies. There had been no operations or serious injuries. The family history was not relevant.

The patient was a well developed young man who seemed to be comfortable. He showed evidence of slight weight loss. No petechiae were noted. The lungs were clear. Blood pressure was 110/80. Pulse rate was 120 and regular. The heart did not seem to be enlarged. A rough, blowing, systolic murmur was heard at the base of the heart. The murmur could also be heard in the neck, the left axilla and at the left lung base. No thrills were palpable. No friction rubs were audible. The spleen was not palpable. Arthritis, subcutaneous nodules or peripheral edema were not present. The remainder of the physical examination was considered normal.

On admission the red blood cell count was 4.7 million per cu. mm., hemoglobin 14.5 gm. per 100 cc., white blood cell count 9,200 per cu. mm. with a normal differential count. The sedimentation rate was normal. Urinalysis and serologic tests for syphilis gave negative results. Throat cultures showed a

* From the Veterans Administration Hospital, Palo Alto, California.

predominance of alpha-hemolytic streptococci. X-ray of the chest showed minimal fibrosis of the right apex without evidence of active disease. Fluoroscopic examination of the chest revealed the cardiac transverse diameter to be within normal limits. The pulmonary artery was prominent, especially in the right anterior oblique position. This region pulsated vigorously. The aorta was comparatively small at the arch. Electrocardiogram showed a sinus tachycardia with inverted T waves in leads 2, 3 and AVF.

The patient was placed on bedrest with symptomatic treatment. He was afebrile the first three days. The pulse rate dropped to 90 to 100. Sedimentation rate and white blood cell count were again normal. Four days after admission the heart murmur changed. Although still of the same intensity, it was now best heard over the pulmonic area. An electrocardiogram at this time showed inverted T waves in leads 2, 3 and AVF, and diphasic T waves in leads V_1 to V_4. The following day a friction rub was audible in the third left interspace. The patient's temperature rose to 100.2°F. Again the white blood cell count and sedimentation rate were normal. On the seventh hospital day the murmur was louder. The friction rub had disappeared. Daily blood cultures taken at this time were reported as negative. The arm-to-lung circulation time was 16 seconds. Venous pressure was 7 cm. of water. Vital capacity was 4,200 cc. On the eighth hospital day the patient was asymptomatic and afebrile. No further change in the murmur was noted. Another electrocardiogram showed inversion of T waves in leads 2, 3, AVF and in leads V_1 to V_4. (Fig. 1.) These changes were interpreted as suggesting diffuse active myocardial or pericardial disease. On the ninth day the patient stated that he felt better. Physical examination was unchanged, and temperature and pulse rate were normal. He was seen early in the evening and no change was noted. Approximately one hour later he was found dead sitting on a toilet.

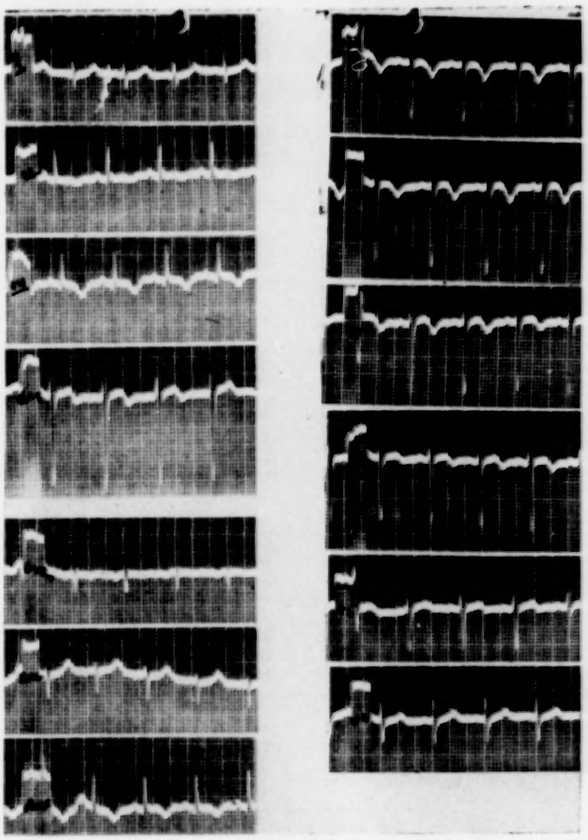


FIG. 1. Case 1. Electrocardiogram taken two days prior to patient's death. Note tendency toward right axis deviation and non-specific T wave changes.

Autopsy revealed that the lungs together weighed 1,075 gm., were congested and edematous. Both the right and left pulmonary arteries were occluded by a large thrombus adherent to the intima at the point of bifurcation. Extensions of the thrombus continued into the larger branches for a distance of 3 cm. (Fig. 2.) Two small infarcts were present at the base of the right lower lobe. The heart weighed 300 gm. The epicardium was dotted with numerous petechiae. The right ventricle appeared dilated and hypertrophied; the left ventricle was moderately hypertrophied. A thrombus was present in the right ventricle, attached only to the chordae tendineae. (Fig. 3.) An attached thrombus was present in the lumen of the left iliac vein, approximately 4 cm distal to the vena cava.

Microscopy disclosed that the lumen of the pulmonary artery was totally occluded by an attached laminated thrombus undergoing organization peripherally. The unattached thrombus in the right ventricle also exhibited evidence of organization. The lungs were markedly congested and edematous. The small infarcts varied in age. One appeared of relatively recent origin; the other showed some peripheral fibrosis. The left iliac vein showed marked thickening with intimal fibrosis and fibroblastic organization of the base of the thrombus. Vasa vasorum in the adventitia exhibited thickening and intimal proliferation. Pathologic diagnoses: (1) thrombophlebitis of the left iliac vein with massive pulmonary embolus, cor pulmonale and small pulmonary infarcts; (2) pulmonary congestion and edema; (3) asphyxial hemorrhages of epicardium.

Comment: This case presents a frequent onset and early course of the syndrome of thrombosis of the major pulmonary arteries. Initially the clinical picture was that of pulmonary infarction with pleuritic pain, dyspnea and fever. The course was somewhat prolonged and was marked by at least one other episode of pulmonary infarction. The loud changing heart murmur associated with x-ray signs of a prominent pulmonary artery and an abnormal electrocardiogram focused attention on the heart. Among the diagnoses considered were congenital heart disease (patent

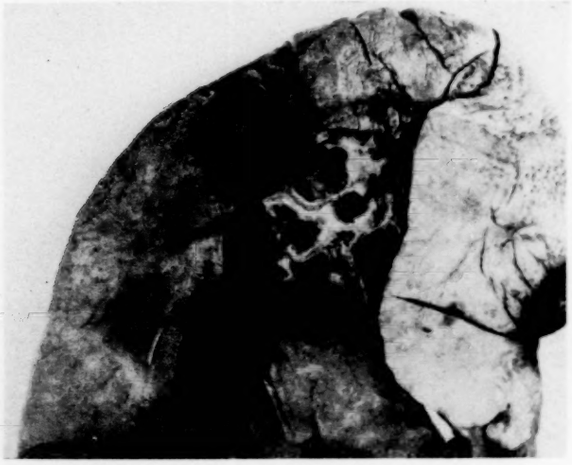


FIG. 2. Same case. Thrombus occluding major pulmonary artery near hilus.

FIG. 3. Same case. Thrombus in right ventricle.

ductus arteriosus or coarctation of the aorta), active rheumatic carditis, bacterial endocarditis or endarteritis, and tuberculous pericarditis. There was no frank congestive heart failure this early in the course.

It was postulated postmortem that part of the original embolus from the iliac vein was caught in the chordae tendineae of the tricuspid valve. The embolus may have projected through the pulmonary valve producing the loud and variable heart murmur. Part of the embolus became adherent to the wall of the pulmonary artery with subsequent organization. Propagation of the thrombus finally resulted in complete occlusion of the pulmonary circulation and sudden death.

CASE II. A. L. K., a thirty-three year old nurse, was admitted to the Veterans Administration, Oakland, on February 7, 1950, complaining of shortness of breath on exertion, cough and tightness in the chest. In February, 1949, she first became aware of shortness of breath and suffered from momentary syncopal attacks. Both symptoms were more frequent after exercise. In March of the same year the right ovary and Fallopian tube were removed for suspected endometriosis. Subsequently she was treated with large doses of male sex hormones from which jaundice developed. In January, 1950, she was told that she had heart trouble and was started on digitalis therapy.

When the patient was twenty-two years of age a rash, enlarged glands, fever and swelling of the joints of the fingers and knees developed which lasted approximately one week. At that time she was told she had an inconsequential heart murmur. Since then she has had no recurrence of joint pain or swelling. The family history was not relevant.

On admission, physical examination revealed a chronically ill young woman with obvious dyspnea, a pulse rate of 98 and a blood pressure of 105/95. Basilar pulmonary rales were present bilaterally. The heart seemed to be enlarged. The cardiac rhythm was regular. A rough systolic murmur was heard over the fourth left interspace and also a diastolic murmur. A questionable thrill was felt over the same area. The second pulmonic sound was accentuated. The liver was felt 5 cm. below the costal margin. The spleen was also palpable.

Numerous laboratory studies were performed. Repeated urinalyses showed 3 to 4 plus albuminuria with hyaline and finely granular casts, a few leukocytes and an occasional erythrocyte. Red blood cell counts and hemoglobin determinations were normal on many occasions. The white blood cell count was usually normal but occasionally rose to 15,000 per cu. mm. The sedimentation rate remained normal throughout this hospital stay. Liver function tests were all normal except for one serum bilirubin determination of 2.5 mg. per cent. A needle biopsy of the liver on March 9, 1950, showed acute and chronic passive hyperemia. Numerous blood cultures were sterile. A biopsy of skin and muscle was normal. Fluoroscopic studies showed moderate left ventricular and left atrial enlargement. A gastrointestinal series, small bowel series, barium enema and intravenous pyelogram were negative. X-ray of the skull was normal. Electrocardiogram repeatedly showed a pattern of right ventricular strain. (Fig. 4.) A stethogram demonstrated the presence of systolic and mid-diastolic murmurs. (Fig. 5.)

Soon after admission pitting edema and ascites developed. The patient was given a low salt diet, diuretics and digitalis with some initial improvement. Two abdominal paracenteses were performed in January and another in March of 1951. No growth was obtained on culturing the fluid. The systolic heart murmur remained unchanged but the diastolic murmur was not always heard. Cardiac catheteriza-

tion studies were done at Mt. Zion Hospital, San Francisco on February 21, 1951. The following results were obtained:

Site	Oxygen (vol. %)	Water Pressure (cm.)
Superior vena cava	10.09	12.0
Right atrium	9.96	11.5
Right ventricle	9.60	62.0
Femoral artery	15.45	

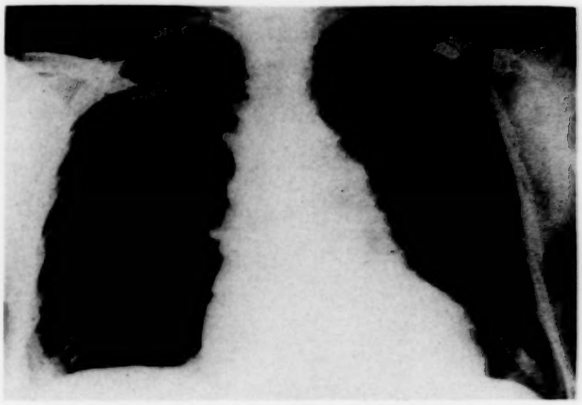
It was thought that these findings indicated either pulmonary hypertension or pulmonary valvular stenosis.

Over the next few months a questionable hepatojugular reflex developed and the patient's blood pressure dropped to 90/70. Three more paracenteses were required, the response to therapy being poor. Three transient episodes of hematuria, frequency and dysuria occurred. In October, 1951, the patient was noted to have periods of confusion and disorientation interspersed with lucid periods. In November she made a suicidal attempt with barbiturates. A diagnosis of schizophrenic reaction was made.

On November 28, 1951, she was transferred to the Veterans Administration Hospital, Palo Alto, for treatment of her mental disorder. She was completely disoriented, confused, had hallucinations and delusions, and exhibited no apparent insight or judgment. Her physical state was much the same as before. A coarse systolic murmur was noted at the apex and a loud systolic murmur over the pulmonic area. A faint diastolic murmur was heard at the fourth left interspace. She had marked peripheral edema, ascites and hepatomegaly. The lungs were clear. It was finally concluded that her psychosis was secondary to cardiac insufficiency associated with prolonged hypoxia of the brain.

Numerous laboratory studies added nothing. X-ray films of the chest continued to show marked right ventricular hypertrophy. Angiocardiography was performed at Stanford University Hospital, San Francisco, on January 10, 1952. This study revealed marked enlargement of the right atrium and ventricle with delay of the dye in these chambers. The pulmonary outflow tract was visualized but the dye did not appear in the pulmonary arteries. (Fig. 6.) The cardioangiogram was interpreted as demonstrating primary pulmonary hypertension with the probability of a thrombus in the right pulmonary artery. During the ensuing five months the patient slowly deteriorated both mentally and physically. She died on July 5, 1952, as a result of congestive heart failure.

Significant findings at autopsy included the following. The body showed evidence of cyanosis and edema of the lower extremities. The peritoneal cavity contained over 5,000 ml. of ascitic fluid. A massive thrombus distended and occluded the pulmonary stem, the right and left pulmonary arteries and all major branches. This thrombus was adherent to the posterior aspect of the bifurcation and the major arteries. The large and medium-sized pul-



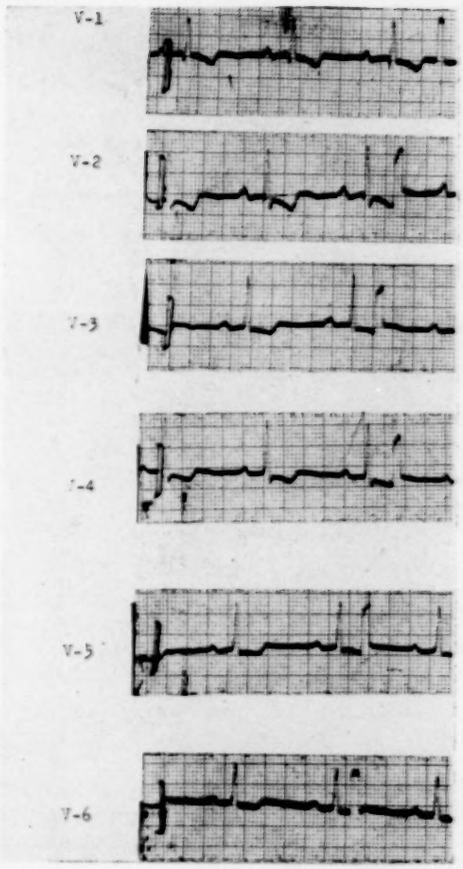


FIG. 4. Case II. Right ventricular enlargement demonstrated by roentgenogram of chest (above) and unipolar chest leads of electrocardiogram (below). Note blunting and dilatation of right pulmonary artery and decreased pulmonary markings.

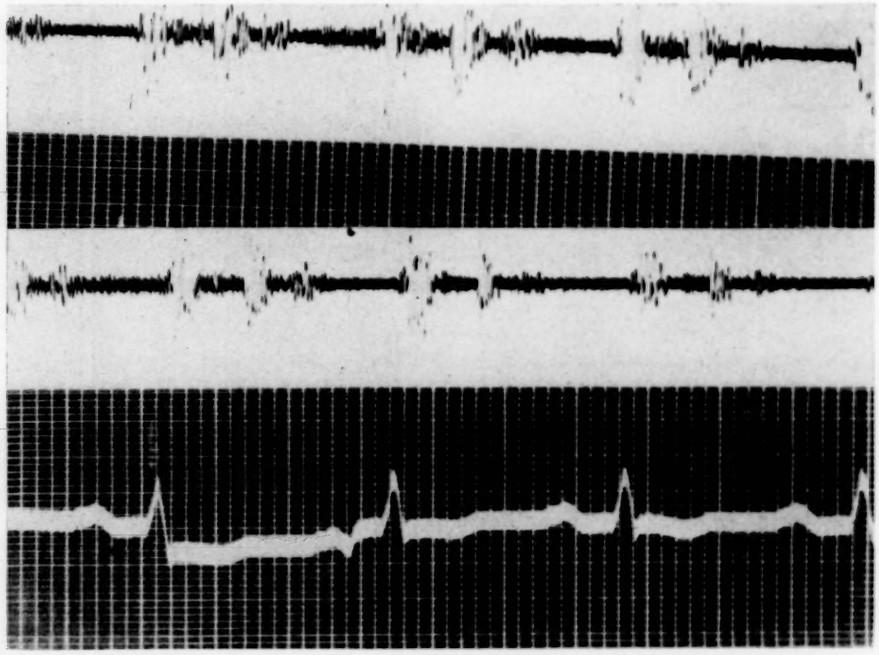


FIG. 5. Same case. Phonocardiogram demonstrating systolic and mid-diastolic heart murmurs.

FIG. 6A. Same case. Angiocardiogram eight seconds after injection of dye. Dye has been delayed in passage with none appearing in the dilated right pulmonary artery. The broken-line markings are due to artefact.

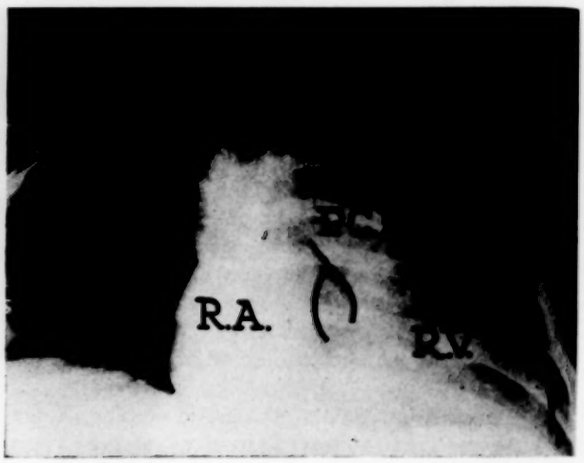


FIG. 6B. Same case. Diagram illustrates structures visualized. R.A., right atrium; R.V., right ventricle; P.C., pulmonary conus.

monary arteries were slightly thickened and irregularly dotted with broad flat atheromatous plaques. Peripheral segments of the arterial tree were normal. The lungs together weighed 790 gm., were mildly edematous and collapsed at the base. The heart weighed 410 gm. and measured 15.5 cm. in transverse diameter. The right atrium was markedly dilated. The right ventricle was moderately dilated and markedly hypertrophied, forming the apex of the heart. The left chambers were small and not seen when the heart was reviewed *in situ*. The right ventricular wall averaged 8 to 9 mm. in thickness and the left, 9 mm. The tricuspid valve measured 12.7 cm. in circumference, the pulmonary 9.0, the mitral 9.1, and the aortic 6.6 cm. No thrombi were present in the right or left chambers. No congenital malformations of the heart were noted. The liver weighed 1,550 gm. The capsule was irregularly thickened and the surface slightly nodular. The organ was firm and cut with slightly increased resistance revealing grayish tan nodules 2 to 7 mm. in diameter bulging from the intervening reddish brown parenchyma. The pattern

FIG. 7A. Same case. Massive thrombus in pulmonary artery. Shows laminated pattern above and organization at base; hematoxylin and eosin stain, × 16½.

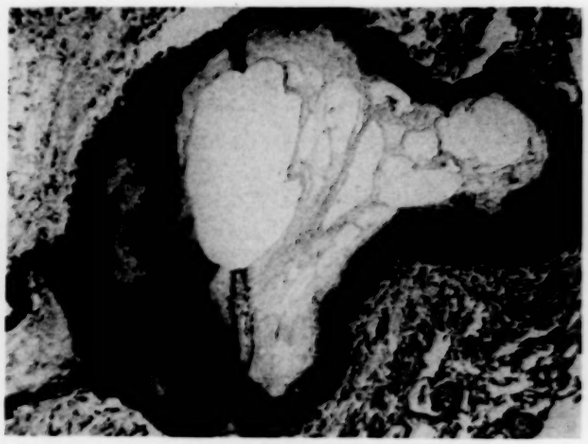


FIG. 8. Same case. Medium-sized pulmonary artery. Lumen partially obstructed by well organized, recanalized thrombus; elastic van Gieson stain, × 70.

FIG. 7B. Same case. Detail from Fig. 7A; hematoxylin and eosin stain, × 70. T, thrombus; O, organization; W, wall of artery.

was finer and the tissue firmer near the capsule. The uterus was small. The right ovary, distal portion of the right Fallopian tube and the appendix were absent. There were fibrous adhesions about the operative site and a phlebolith was present in one of the local vessels. The aorta was studded with flat atheromas, most numerous in the abdominal segment. No thrombi were found in the large veins. There was generalized passive hyperemia. Clusters of petechiae were present on serous surfaces, the gastric mucosa, and in the periesophageal and peritracheal connective tissues.

Microscopic examination showed that the massive thrombus in the large pulmonary arteries had a well defined trabecular pattern superficially and an amorphous appearance near the base which exhibited varying degrees of organization. (Fig. 7.) The intima was studded with numerous moderately thick atheromatous plaques showing rare foci of calcification. The media was thinned, extensively vascularized, and infiltrated with polymorphonuclear leukocytes, small and large mononuclear cells. Elastic fibers appeared markedly compressed and focally absent; smooth muscle was partially replaced with fibrous tissue. The adventitia was greatly thickened by dense collagen. The vasa vasorum were ectatic and, in places, were surrounded by extravasated blood. Focal lymphocytic infiltrations dotted the adventitia. A few of the small elastic arteries were partially obstructed by well organized, widely recanalized thrombi. (Fig. 8.) The intima of most arteries 1 mm. or greater in diameter was irregularly widened by fibrous hyperplasia and focal collection of foamy phagocytes. The muscular arteries were not altered. Only rare arterioles appeared thickened and narrowed. The lungs exhibited focal collapse, hyperemia and mild edema. Small numbers of erythrocytes and brown pigment-laden phagocytes were scattered through the alveoli. Myocardial fibers of the right ventricle were hypertrophied, contrasting with those of the left ventricle which often appeared shrunken. On the right there was focal fibrous thickening of the endocardium and one small unattached laminated thrombus was trapped between columnae carneae. The liver showed marked centrolobular congestion

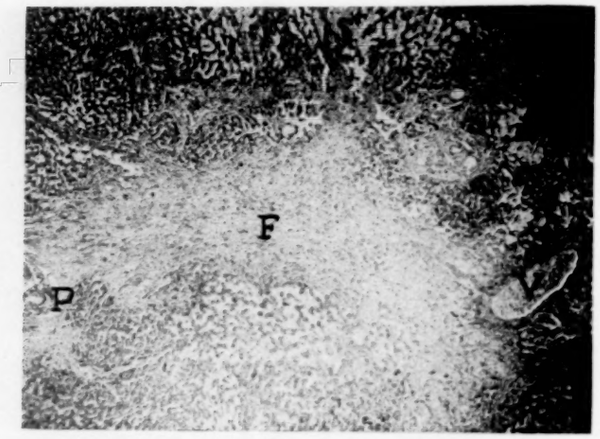


FIG. 9. Same case. Congestive cirrhosis of liver; hematoxylin and eosin stain, × 70. S, congested sinusoids; P, portal area; F, fibrous scarring; V, thickened, engorged branch of hepatic vein.

with atrophy and focal degeneration. Bile pigment granules were present intracellularly and small bile thrombi in canaliculi. The lobular architecture was grossly distorted by patchy fibrosis, primarily central in distribution, obliterating central veins and often assuming a scalloped or stellate pattern. (Fig. 9.) Numerous proliferated small bile ducts, a few lymphocytes and occasional hepatic cells were buried in the fibrous scar tissue which was most extensive in the subcapsular zone. Renal tubular degeneration was widespread and moderately severe involving various segments of the nephron. Glomeruli exhibited mild nuclear proliferation. Small and a few moderate-sized atheromas were scattered through the intima of the aorta, resulting in mild medial compression. Serosal surfaces of the viscera were dotted with small foci of chronic inflammatory reaction. The brain exhibited no signs of hypoxic or vascular change.

The pathologic diagnoses were: (1) chronic massive thrombosis of pulmonary artery and major branches, (?) embolic from pelvic veins; (2) secondary pulmonary hypertension (clinical diagnosis) with marked hypertrophy and dilatation of right heart, passive hyperemia, congestive cirrhosis of the liver, marked ascites, moderate edema of lower extremities, moderately severe renal tubular degeneration, and petechial hemorrhages focally; (3) moderate arteriosclerosis of large and medium-sized pulmonary arteries; (4) absence (surgical) of right ovary, tube and appendix with local phlebolith and fibrous adhesions.

Comment: In this case the presenting problem was progressive right ventricular failure of undetermined origin. Diagnoses considered were carditis associated with rheumatic fever or lupus erythematosus, pulmonary stenosis and constrictive pericarditis. Congestive failure was accompanied by the development of congestive cirrhosis and hypoxic psychosis. Catheterization of the heart pointed to a disturbance of the pulmonary circulation. Angiocardiography established the diagnosis of occlusion of the right pulmonary artery. By the time the latter diagnosis was made the poor condition of the patient precluded surgical intervention.

The origin of the pulmonary thrombus could not be established definitely but was assumed to be an embolus originating in the pelvic veins. However, pulmonary arteriosclerosis or arteritis could not be ruled out as possible factors. The congestive heart failure existed for thirty months prior to death.

DISCUSSION

Prior to 1941 a total of 100 case reports of this syndrome had been published. Since then thirty-one additional cases and two collected series of fourteen cases each have appeared in the American and European literature. Thus it is probable that no more than 200 cases of the syndrome have been reported in medical literature to date.

The incidence of a condition cannot be estimated reliably from the number of cases reported. Some clues concerning frequency can be derived from the two largest series reported. One group of fourteen cases was accumulated from 706 autopsies.[3] The other series of fourteen cases was derived from admissions to a 335 bed, teaching hospital over a ten-year period.[4] Such experience suggests that the syndrome occurs more frequently than the total number of case reports indicate. Furthermore, a study of 100 consecutive unselected autopsies revealed four cases of thrombosis of the major pulmonary arteries associated with acute embolism.[5] If any of these patients had survived long enough for attachment and organization of the thromboembolus to occur, it is likely that this clinical syndrome would have followed.

The clinical syndrome exhibits no specific diagnostic features. The following diagnostic triad has been proposed: (1) an episode resembling pulmonary infarction, (2) disclosure of the source of embolism and (3) progressive right ventricular failure.[3] However, symptoms or signs of thromboembolic disease can be elicited in only about half of these patients. Certain other clinical features may serve to bring this condition to mind: (1) heart failure of obscure cause in young persons; (2) marked right-sided heart failure (peripheral edema and ascites) with little left-sided failure (dry lungs); (3) poor response to the usual therapy for cardiac failure: (4) the frequent appearance of a systolic heart murmur and, occasionally, a diastolic or continuous murmur;[6–8] and (5) syncopal attacks or

mental symptoms occurring in the course of congestive failure.

The diagnostic tools of cardiology are extremely helpful in these cases. The classic roentgen signs of thrombosis of the major pulmonary arteries have been summarized as follows: (1) dilatation of the pulmonary artery proximal to the block, (2) enlargement and alteration in the contour of the vessel at the level of the thrombus, and (3) decrease in the caliber of vessels distal to the thrombus, resulting in increased radiolucency in the corresponding area of lung.[6,9] Cardiac catheterization led to the first antemortem diagnosis which was confirmed by surgical exploration and biopsy of the occluded pulmonary artery.[10] Since 1951 angiocardiography has been used to confirm the antemortem diagnosis.[11–13] Roentgenologic and electrocardiographic evidence of right ventricular enlargement is common. Measurements of venous pressure, circulation time and vital capacity may aid in the early detection of congestive failure in these patients. Despite the frequency of cyanosis, polycythemia has been uncommon.

Rheumatic, congenital and arteriosclerotic heart disease frequently enter into the differential diagnosis of this syndrome. The close association with mitral stenosis, so commonly noted in the past, no longer holds. Concurrent congenital heart disease may be present.[14,15] In one instance the syndrome was due to a congenital anomaly of the pulmonary artery.[16] Although arteriosclerosis of the coronary artery is often considered in the differential diagnosis, it is seldom an associated finding. In one patient the syndrome was ascribed to embolization of a mural thrombus following silent myocardial infarction.[17] The occasional occurrence of fever in these patients has resulted in confusion with bacterial endocarditis[18] or pulmonary infectious disease.[19] Other conditions which have been considered in the differential diagnosis include chronic cor pulmonale due to pulmonary degenerative disease, acute cor pulmonale associated with pulmonary infarction, constrictive pericarditis, beriberi and traumatic aneurysm.

The major cause of this syndrome is now attributed to embolism rather than a complication of pulmonary arteriosclerosis, chronic pulmonary disease or mitral stenosis. Trauma, either directly to the chest[12,13,19] or as a cause of remote phlebitis and embolism,[18] has been recognized as etiologic, especially in younger persons.

The introduction of anticoagulant and enzyme therapy has made possible some degree of prevention and control of thromboembolic disease. More important, the rapid progress of cardiovascular surgery has made it possible to treat some of these patients surgically. At least one patient with this syndrome has been cured by surgery.[20] He underwent pneumonectomy for a suspected aneurysm of the pulmonary artery, with removal of the involved segment of the vessel. Embolectomy or endarterectomy would have been preferable. If this syndrome is detected early enough, and the means for so doing are now available, more patients should be cured.

SUMMARY

Two cases of thrombosis of the major pulmonary arteries are presented. One, illustrating the onset and early development of the syndrome, presented as a case of pulmonary infarction with baffling cardiac signs. Sudden death ensued after a short course. The other ran a chronic course with the development of right ventricular failure, congestive cirrhosis and psychosis. Angiocardiography in the latter case led to the correct diagnosis prior to death.

Clinical features which suggest the diagnosis are: (1) history of thromboembolic disease; (2) progressive marked right ventricular heart failure of obscure cause responding poorly to therapy; (3) dry lungs despite the presence of dyspnea, cyanosis, peripheral edema and ascites; (4) new or changing heart murmurs; (5) syncopal attacks or periods of mental confusion during the course of the illness.

Roentgen studies are invaluable in making the diagnosis. Routine x-rays of the chest frequently demonstrate blunting or deformity of one or both pulmonary arteries associated with diminution in the vascular markings of the lung. Angiocardiography can be used to confirm the presence of occlusion of the pulmonary artery.

There is reason to believe that this syndrome occurs more often than indicated by the number of cases reported. Only one patient is known to have been treated successfully. However, recent advances in cardiovascular surgery, the development of anticoagulants, and perhaps enzyme therapy should achieve effective treatment of more patients with this syndrome.

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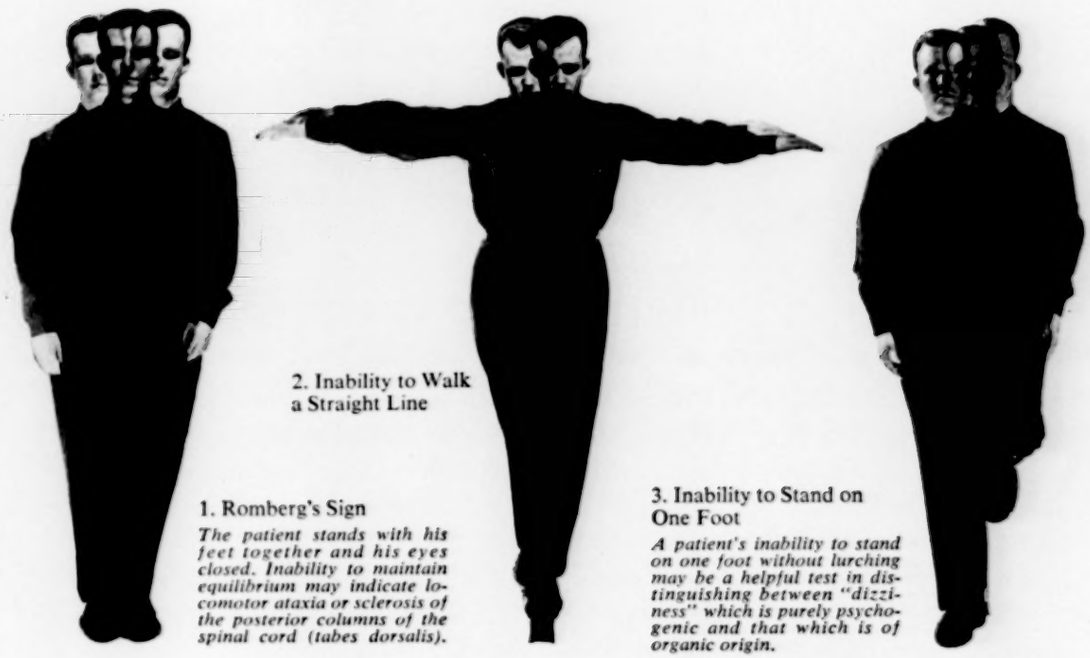
Notes on the Diagnosis and Management of "Dizziness"

II. False Dizziness



2. Inability to Walk a Straight Line

1. Romberg's Sign

The patient stands with his feet together and his eyes closed. Inability to maintain equilibrium may indicate locomotor ataxia or sclerosis of the posterior columns of the spinal cord (tabes dorsalis).

3. Inability to Stand on One Foot

A patient's inability to stand on one foot without lurching may be a helpful test in distinguishing between "dizziness" which is purely psychogenic and that which is of organic origin.

False dizziness is a sensation of sinking or lightheadedness which is often of psychogenic origin. It should be distinguished from true "dizziness" or vertigo[1] in which there is a definite whirling, moving sensation.

Unsteadiness, lightheadedness and similar manifestations of false dizziness[2] may be psychogenic or the result of arteriosclerosis, hypoglycemia, drug sensitivity and general metabolic disturbances such as anemia and malnutrition. Hypertension is often the cause of these symptoms.

Psychogenic dizziness probably originates at the highest brain centers. It may be described as a sense of uncertainty with occasional mild lurching but not to the point of falling. In these patients there is no nausea, no disturbance of vestibular pathways and otologic and neurologic examinations are negative. The sensation is unaffected by head movement. Symptoms usually disappear[3] with complete rest.

Dramamine® has been found highly effective in many of the conditions already mentioned. Maintenance therapy with Dramamine will often keep the patient from becoming incapacitated by his condition.

Dramamine is also a standard for the management of motion sickness and is useful for relief of nausea and vomiting of fenestration procedures and radiation sickness and for relief of "true dizziness" of other disorders.

Dramamine (brand of dimenhydrinate) is supplied in tablets (50 mg.) and liquid (12.5 mg. in each 4 cc.). G. D. Searle & Co., Research in the Service of Medicine.

1. Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

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SEARLE

What do you want in an analgesic?

Percodan®*

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

FOR PAIN

Better than codeine plus APC

speed acts faster than codeine plus APC—usually within 15 minutes[1, 2]

duration relieves pain longer than codeine plus APC—usually for 6 hours with virtual freedom from constipation[1, 2]

Average adult dosage, 1 tablet q. 6 h. Supplied as scored, yellow oral tablets. May be habit-forming. Literature? Write—

Endo®

ENDO LABORATORIES INC. Richmond Hill 18, New York

1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.
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*U.S. Pat. 2,628,185

Meat...

and the Hot-Weather Diet

Contrary to opinion in former years, meat is fully as well suited to the diet in the heat of summer as in the cold of winter.[1] Except for a possibly lessened need for calories and a greater need for water and salt (to compensate for losses in perspiration), the requirements for essential nutrients—protein, vitamins, and minerals—to all intents and purposes remain the same during the hot months as during the cold.

The metabolism of protein supplied by the mixed diet develops less heat requiring dissipation by the body than when the same amount of protein is fed alone.[2,3]

A protein-high diet exerts little if any effect upon work efficiency during hot weather. Meat eaten by workers acclimatized to a hot, humid environment produces no discernible untoward effects.[4]

Meat, providing large amounts of protein similar to human protein in kinds and proportions of contained amino acids,[5] constitutes a year-round food of high nutritional value. It is also a good source of B vitamins and essential minerals—iron, phosphorus, potassium, and magnesium. It is equally nutritious whether eaten hot or cold.

---

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The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

HOW OLD IS OLD?

"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adoléscence and senescence."[3]

"One finds alert, interesting, active folks in the 80's and, on the other hand, there are people in the 20's and 30's who have all the characteristics of old age."[4]

THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth – perhaps most important – is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

NEOBON'S COMPREHENSIVE FORMULA

NEOBON®, a product of Roerig research, is a blended combination of the five most commonly indicated factors for prevention or treatment of the nonacute conditions of aging. Each soft, soluble capsule provides:

Non-stimulatory gonadal hormone replacement

balanced hematinic component

digestant enzyme replacement

specially formulated mineral-vitamin combination

new lysine, for protein improvement*

* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics." Such people have much to gain from NEOBON therapy. The rewards are fuller, more active, more pleasurable years for patients past 40. The daily dose (3 capsules) of NEOBON provides:

L-lysine	150 mg.
Methyltestosterone	3 mg.
Ethinyl Estradiol	0.018 mg.
Pancreatic Substance***	150 mg.
Glutamic Acid	90 mg.
Rutin	15 mg.
Vitamin A (Palmitate)	6,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	600 U.S.P. Units
Vitamin E (as Tocopheryl Acetate)	15 I.U.
Calcium Pantothenate	15 mg.
Thiamine Mononitrate (Vitamin B_1)	1.5 mg.
Riboflavin (Vitamin B_2)	1.5 mg.
Pyridoxine Hydrochloride (Vitamin B_6)	1.5 mg.
Niacinamide	150 mg.
Ascorbic Acid (Vitamin C)	150 mg.
Vitamin B_{12} (Oral Concentrate)	3 mcg.
Folic Acid	0.3 mg.
Liver-Stomach Substance**	300 mg.
Iron (from Ferrous Gluconate)	10.2 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Potassium (from Potassium Sulfate)	5 mg.
Zinc (from Zinc Sulfate)	1.2 mg.

**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.

***Enzymatically active defatted material obtained from 750 mg. of whole fresh pancreas.

Dosage: 3 capsules daily, with meals.

Supplied: Bottles of 60 capsules, prescription only.

NEW NEOBON® LIQUID

A GERIATRIC TONIC

Now also available for your consideration is NEOBON LIQUID, which provides hematinic action, improved carbohydrate and protein utilization, gonadal and thyroid hormone supplementation and a mild antidepressant action.

The pleasant tasting liquid is especially indicated when a combined attack against nutritional, physiological and mental depression is indicated. Each teaspoonful (5 cc.) of pleasant-tasting NEOBON LIQUID contains:

Ferrous Gluconate	30 mg.
Ascorbic Acid	50 mg.
d-Amphetamine Sulfate	0.5 mg.
Folic Acid	167 mcg.
Vitamin B_{12}	2.5 mcg.
l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

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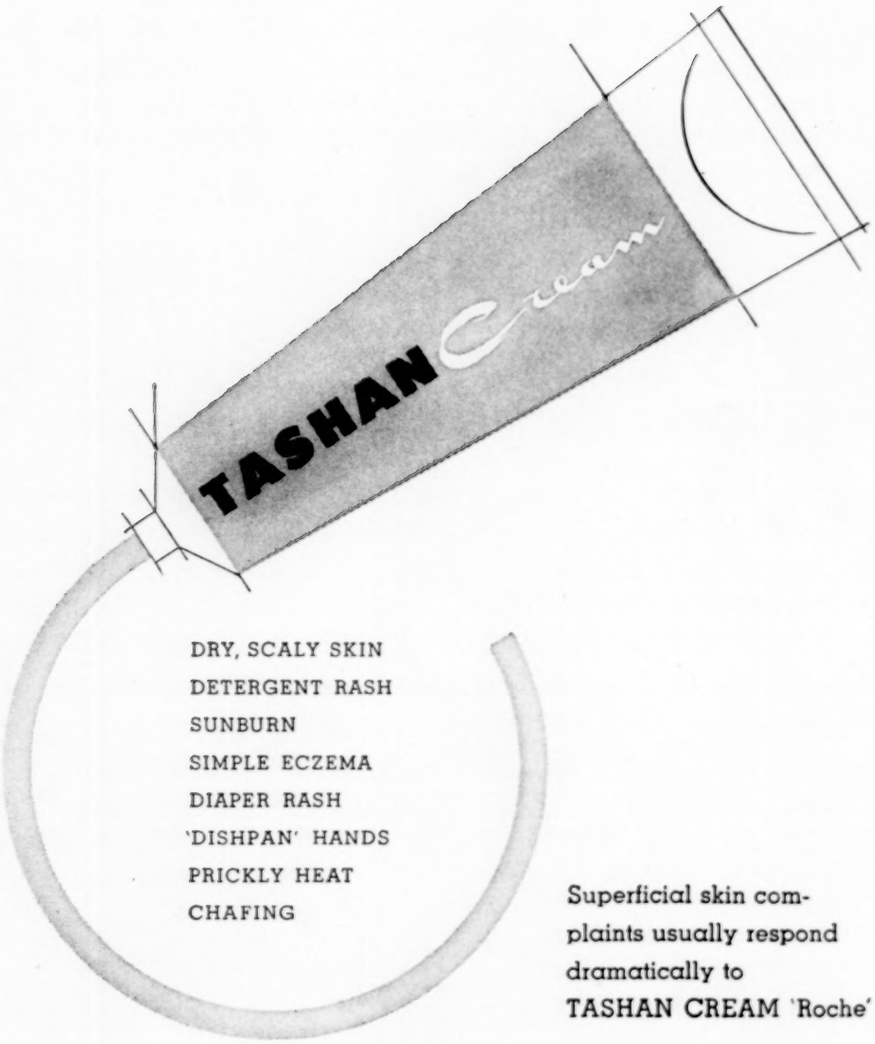
ROERIG Rx *CHICAGO 11, ILLINOIS*



Superficial skin complaints usually respond dramatically to TASHAN CREAM 'Roche'

Antiprurient, soothing, and healing—contains vitamins A, D, E, and *d*-Panthenol, in a cosmetically pleasing water-soluble base which fastidious patients will enjoy using. Hoffmann-La Roche Inc., Nutley, N. J.

TASHAN T. M.

Enriched Bread... and Child Health in America

The enrichment of commercial white bread with thiamine, riboflavin, niacin, and iron is one of the important factors in the improvement of nutrition in America's school children.[1] Improved nutrition appears to have made a valuable contribution to the improvement of child health during recent years.[2]

Containing nonfat milk solids (usually 4 lbs. per 100 lbs. of flour) as well as officially defined amounts of B vitamins and iron, enriched bread provides high percentages of recommended daily dietary allowances for children.

The protein of enriched bread, an aggregate of flour, milk, and yeast proteins, is high in nutritive quality, effective for growth as well as tissue maintenance. On the basis of its percentage of calories provided, enriched bread supplies substantially more than its share of niacin, thiamine, and iron, and a goodly proportion of riboflavin and calcium. Because enriched bread presents carbohydrate and good quality protein simultaneously, the carbohydrate thereby "sparing" protein, it helps promote optimum protein anabolism.[3] For all these reasons, enriched bread constitutes a valuable asset to good nutritional health in children.

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Percentages of Recommended Daily Dietary Allowances* for Children Provided by Enriched Bread—6 and 8 slices

	Children Ages 4 to 6 years		Children Ages 7 to 9 years	
	6 slices	8 slices	6 slices	8 slices
Protein	23%	31%	20%	26%
Niacin	38	50	30	40
Riboflavin	18	23	14	19
Thiamine	41	55	33	44
Calcium	12	16	12	16
Iron	41	55	33	44
Calories	24	32	19	25

*National Research Council's recommended daily dietary allowances (1953):
Children, 4 to 6 years of age; weight, 40 lbs.; height, 43 inches.
Children, 7 to 9 years of age; weight, 59 lbs.; height, 51 inches.

AMERICAN BAKERS ASSOCIATION
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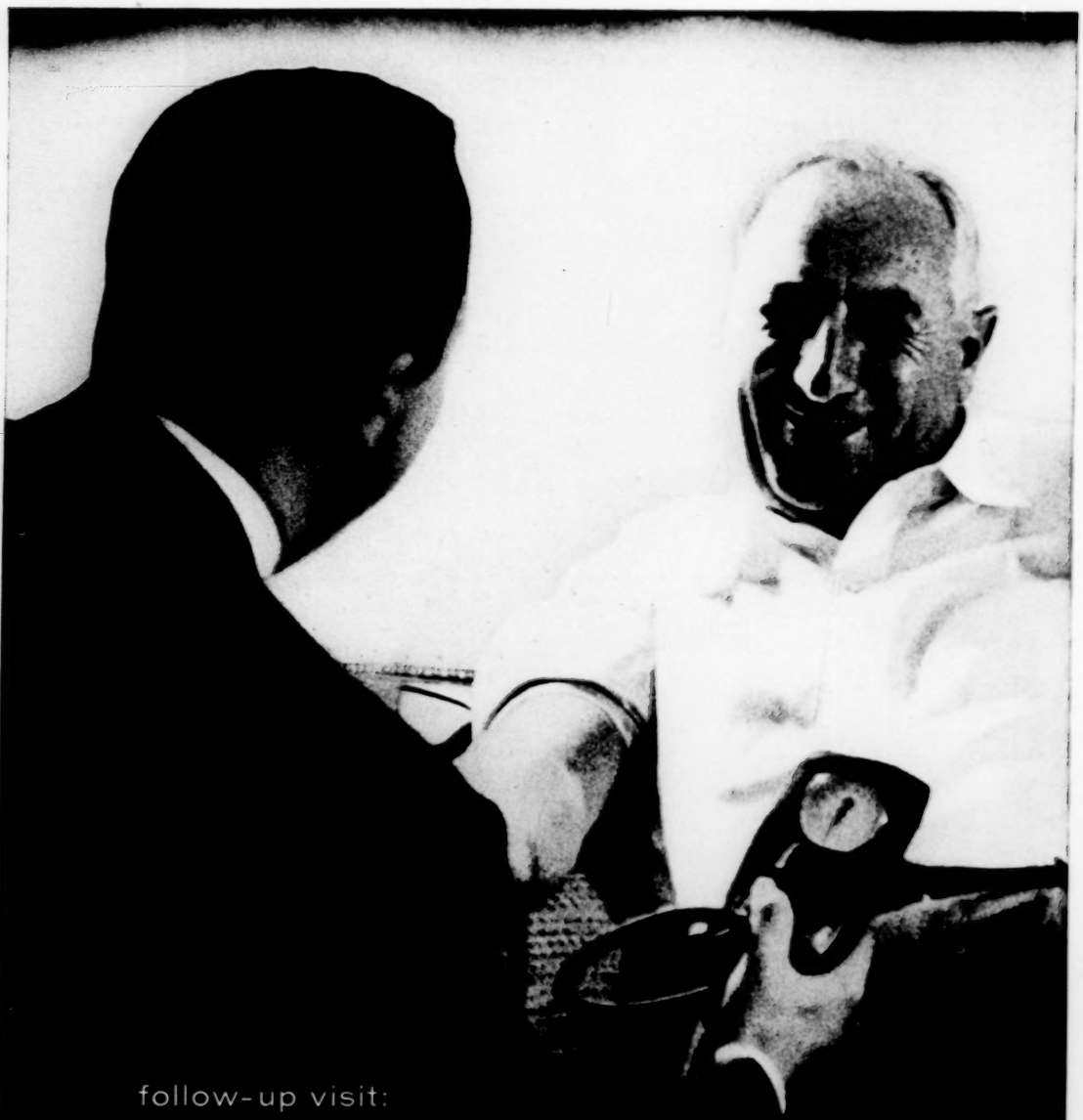
The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



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lowers the systolic *and* especially the clinically more significant *diastolic* pressure

increases renal and cerebral plasma flow

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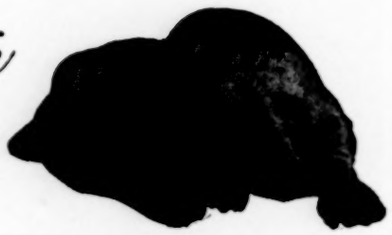

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Available as ELIXIR ALURATE, cherry red color/ELIXIR ALURATE VERDUM, emerald green color
Each contains 0.03 Gm (½ grain) of Alurate per teaspoonful (4 cc)
in a palatable vehicle. Alurate®—brand of aprobarbital

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August, 1956